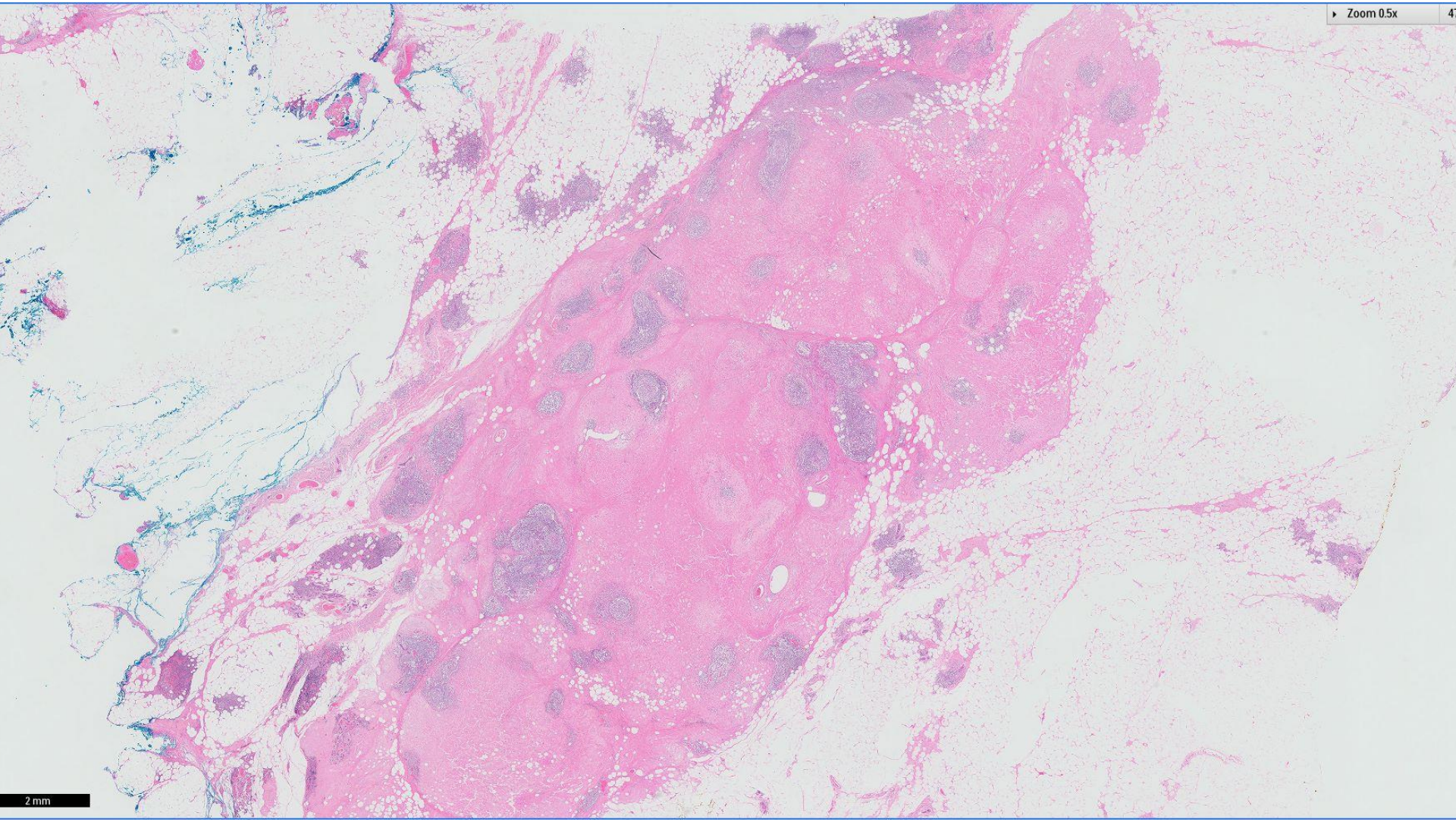
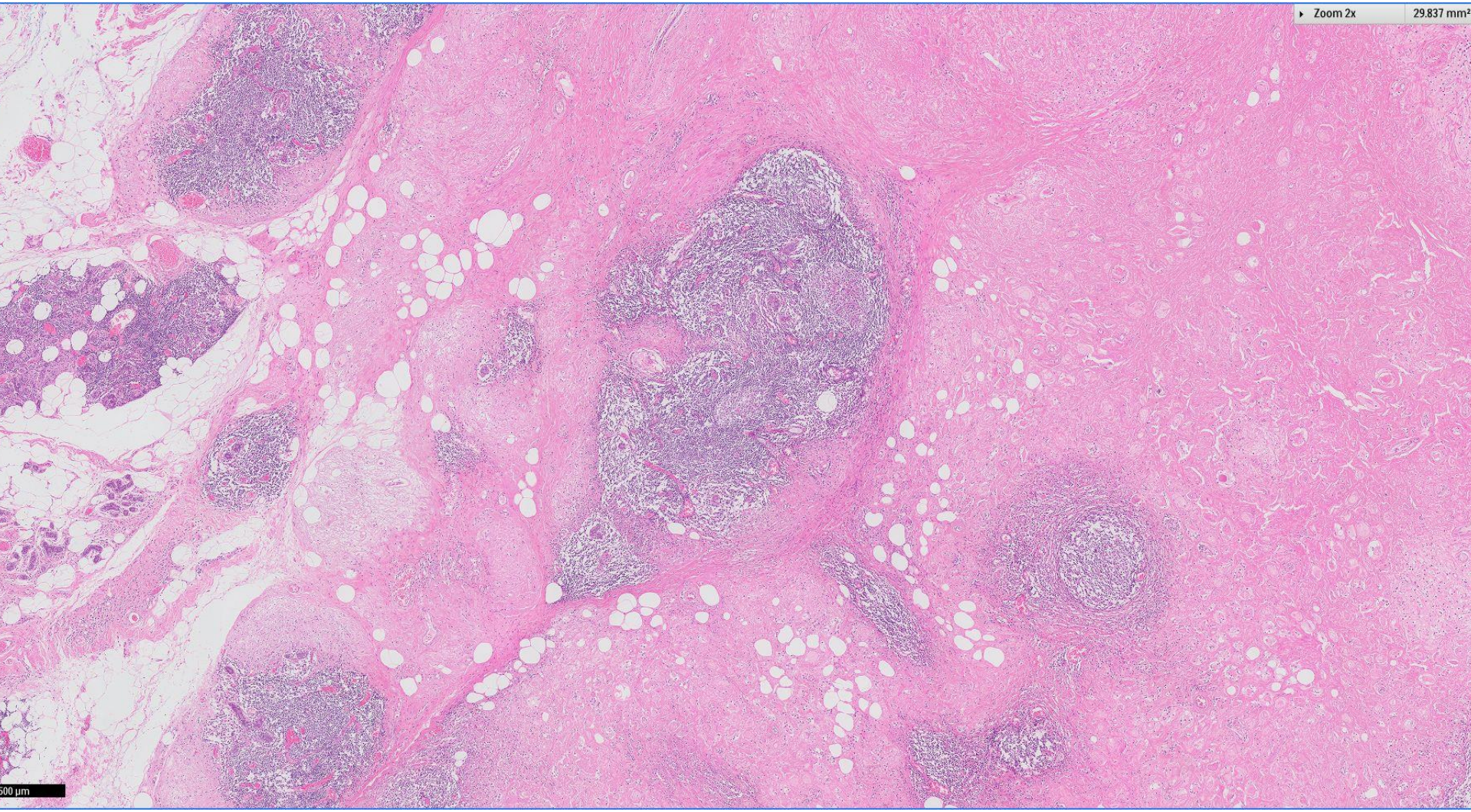
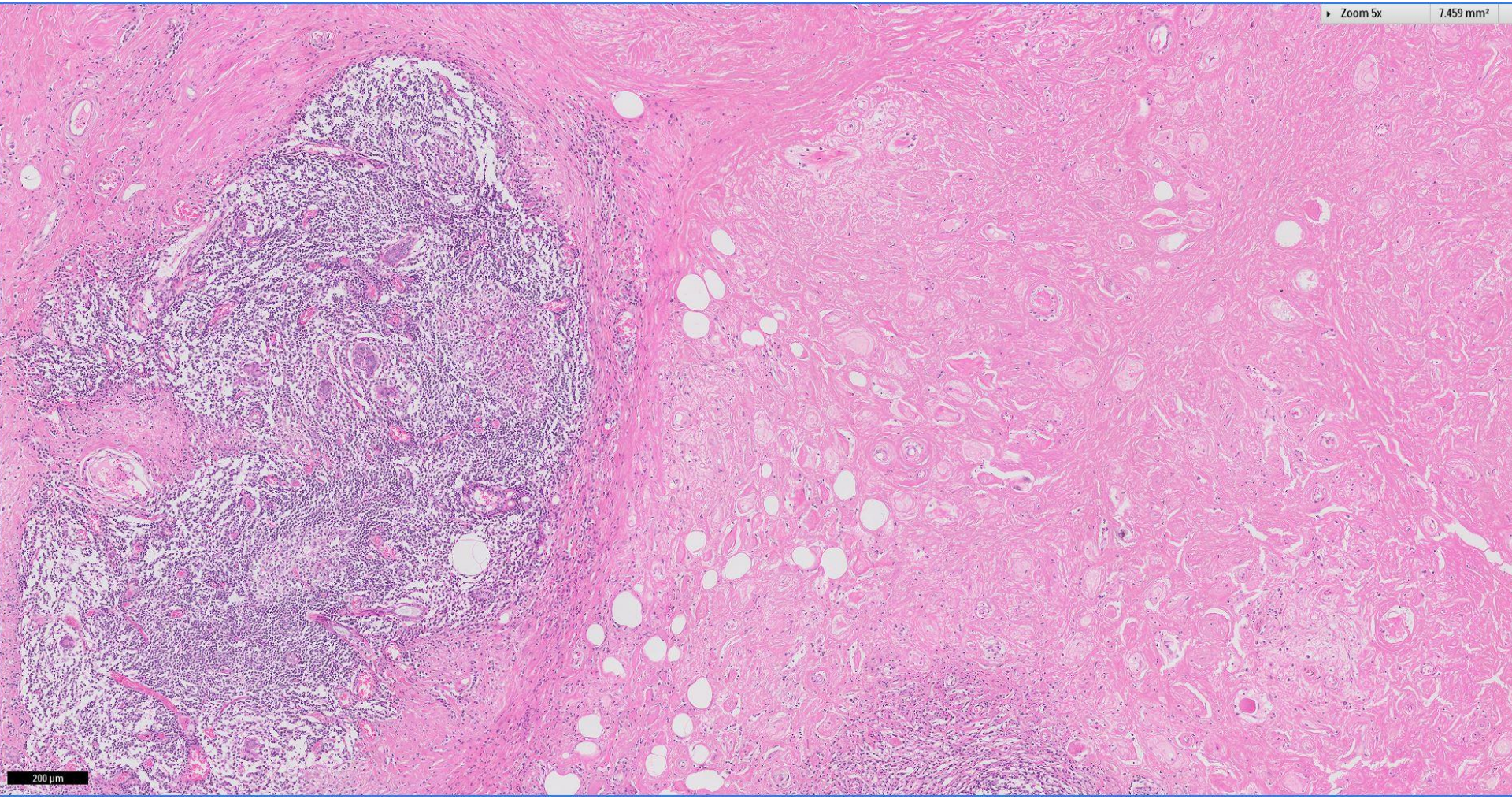
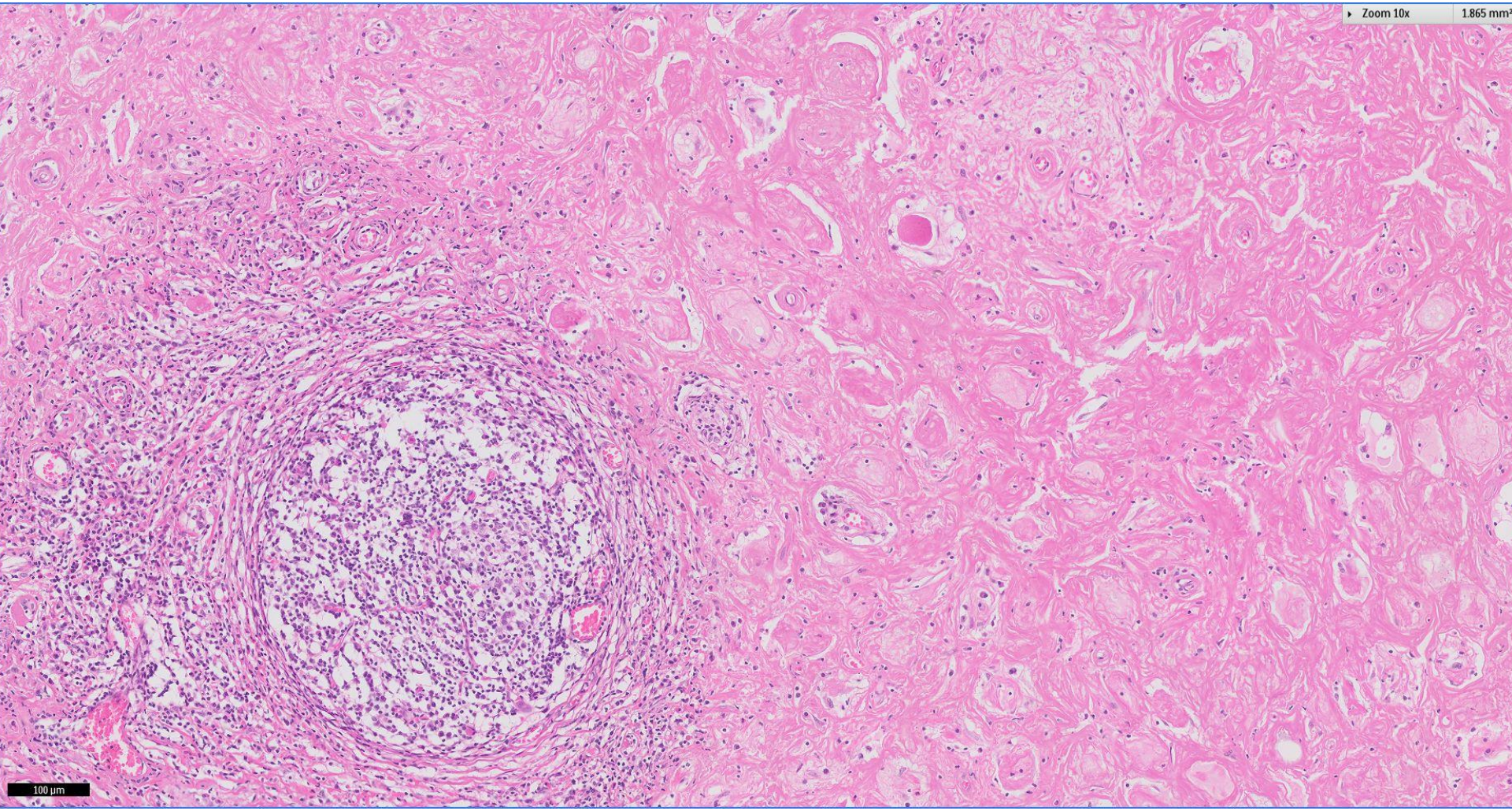
Case 31

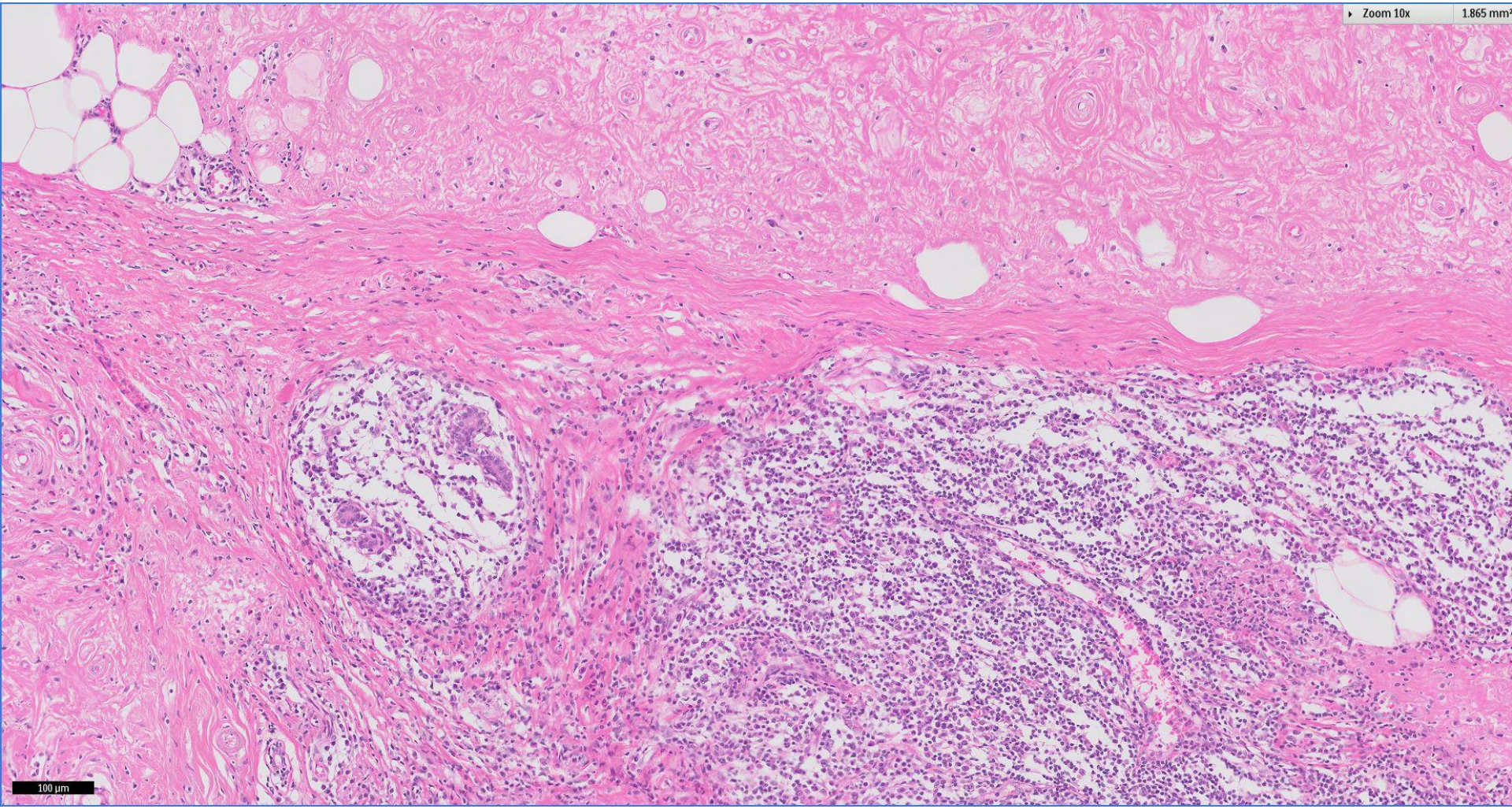
59 year old woman presented with a right breast lump for which wide excision was performed. There was a past history of renal cell carcinoma.


Zoom 0.5x
2 mm


Zoom 2x
29.837 mm²
500 µm


Zoom 5x
7.459 mm²
200 µm


Zoom 10x
1.865 mm²
100 µm


Zoom 10x
1.865 mm²
100 µm

5TH SINGAPORE GENERAL HOSPITAL BREAST PATHOLOGY COURSE 2014

Timely Topics in Breast Pathology

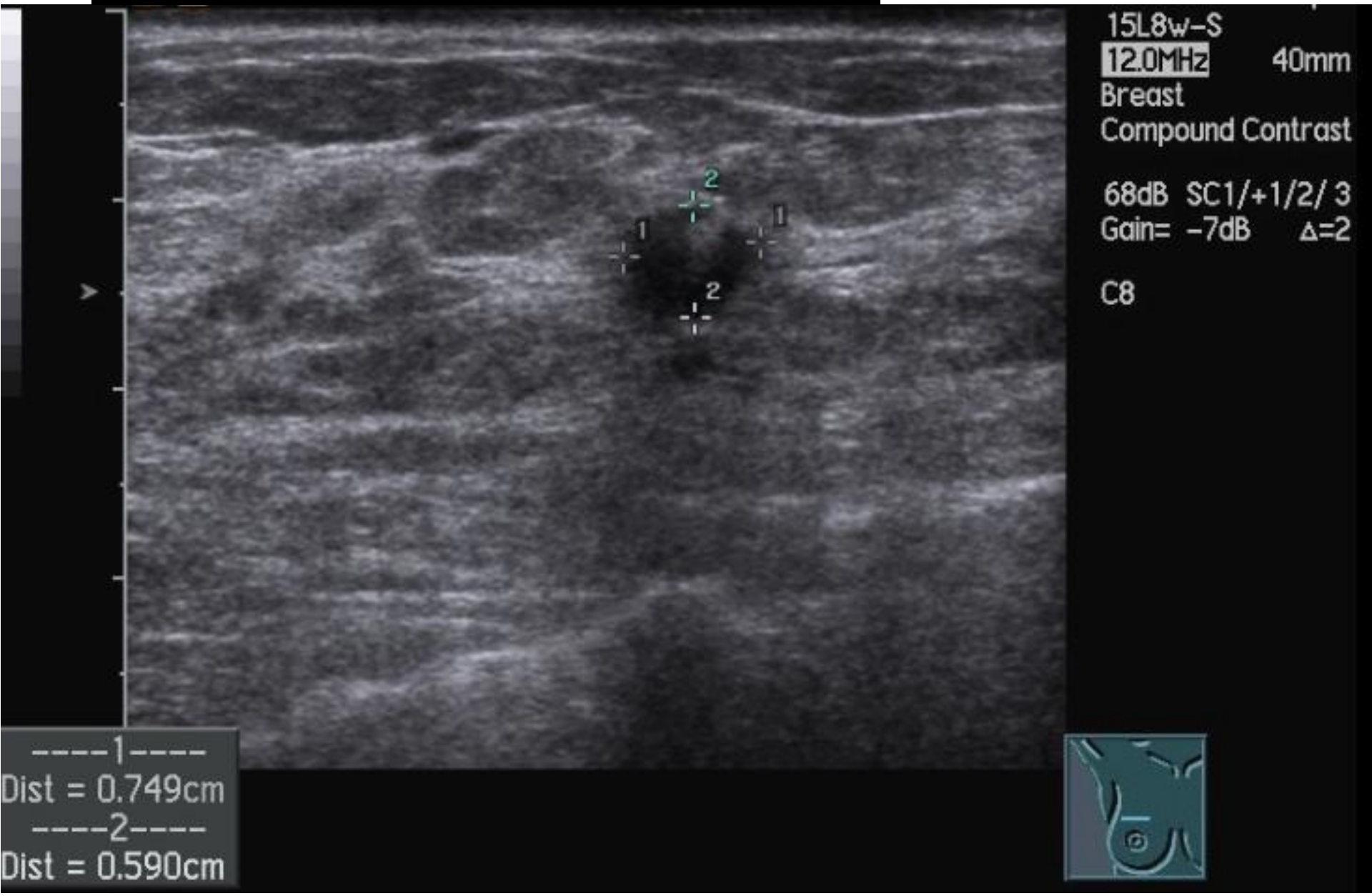
SINGAPORE GENERAL HOSPITAL
DEPARTMENT OF PATHOLOGY
21st & 22nd NOVEMBER 2014

MAGNET RECOGNIZED
AMERICAN NURSES CREDENTIALING CENTER

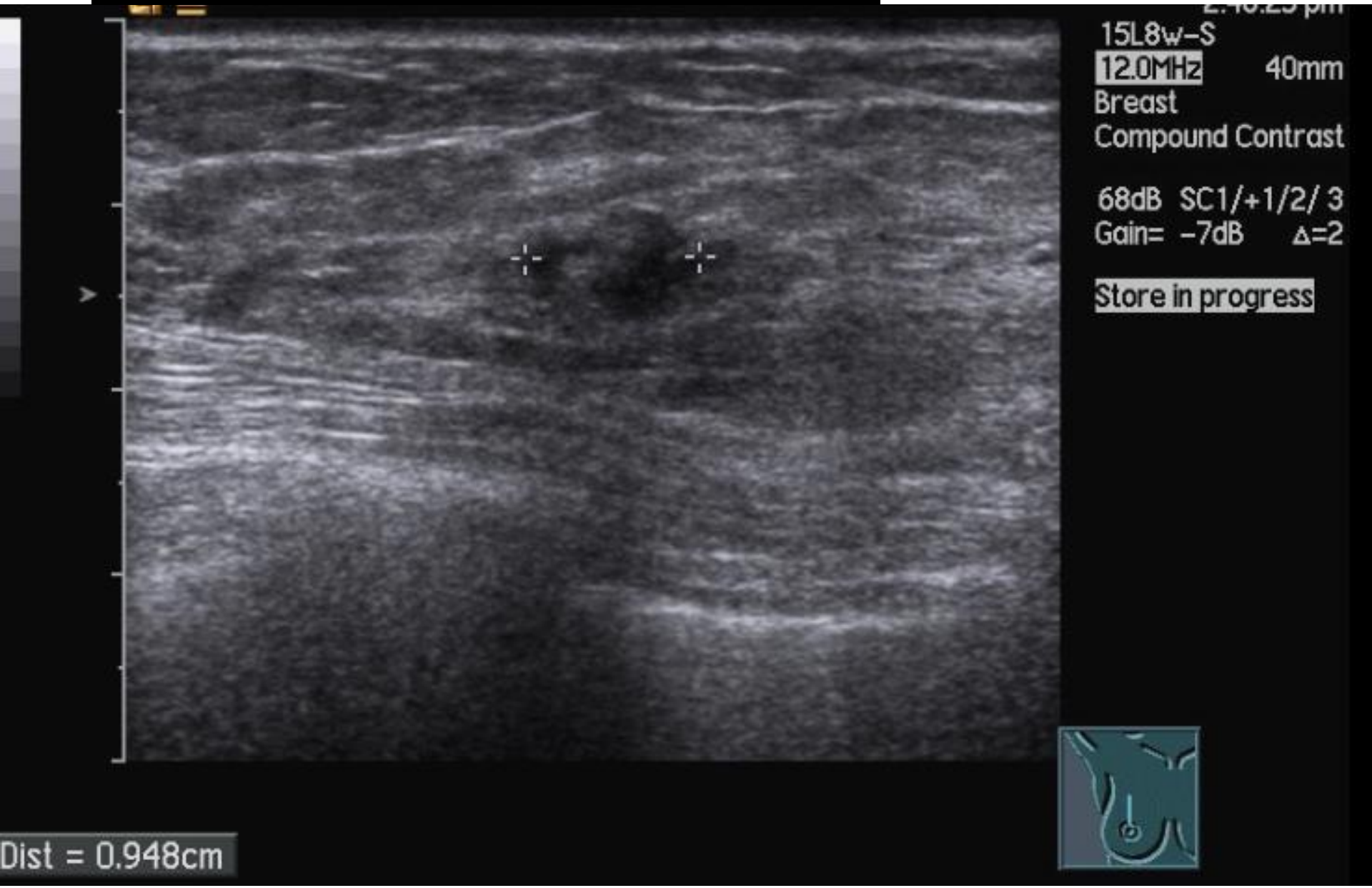
Singapore General Hospital
SingHealth

Case 31

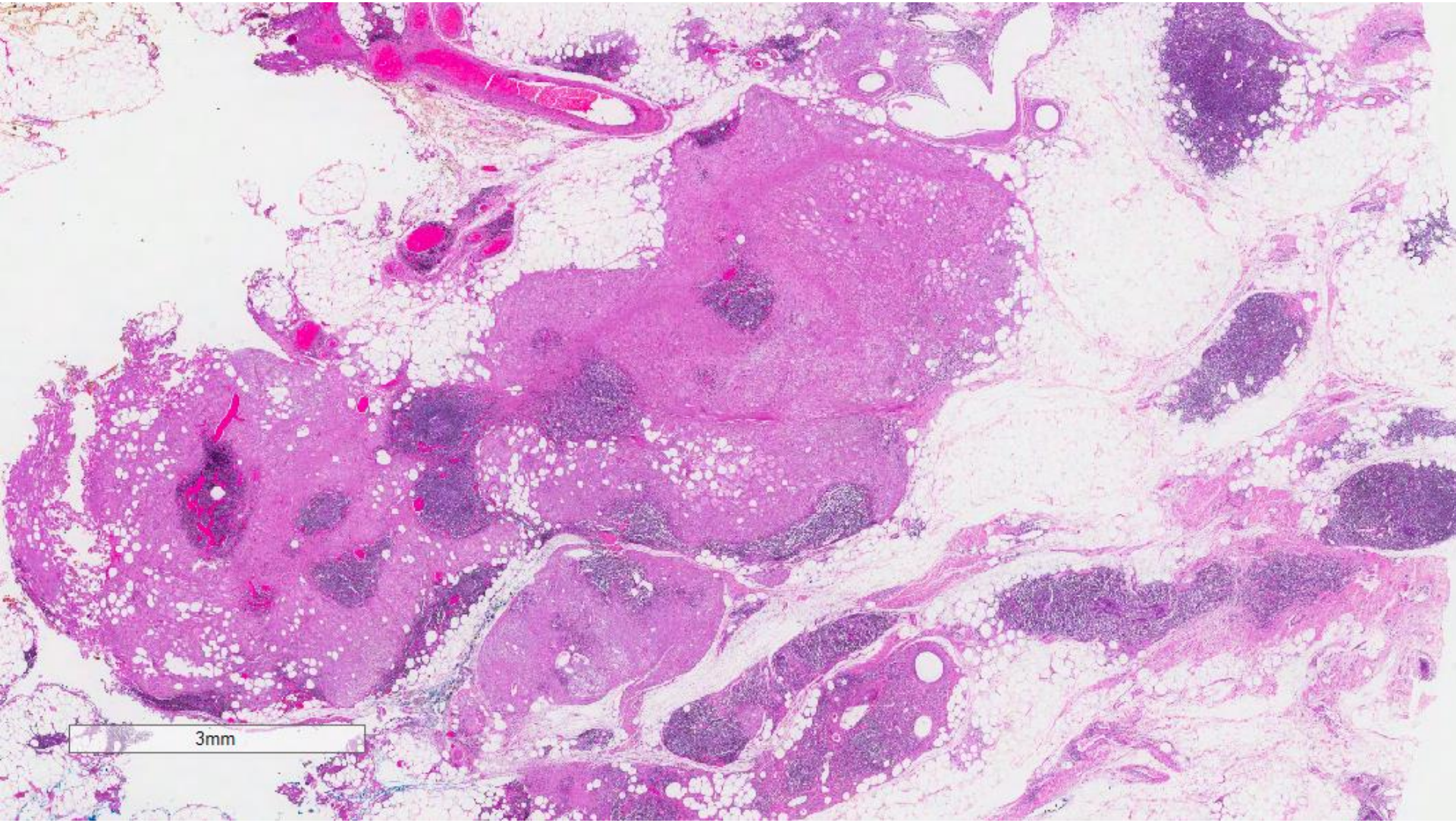
March 2010, right breast ultrasound



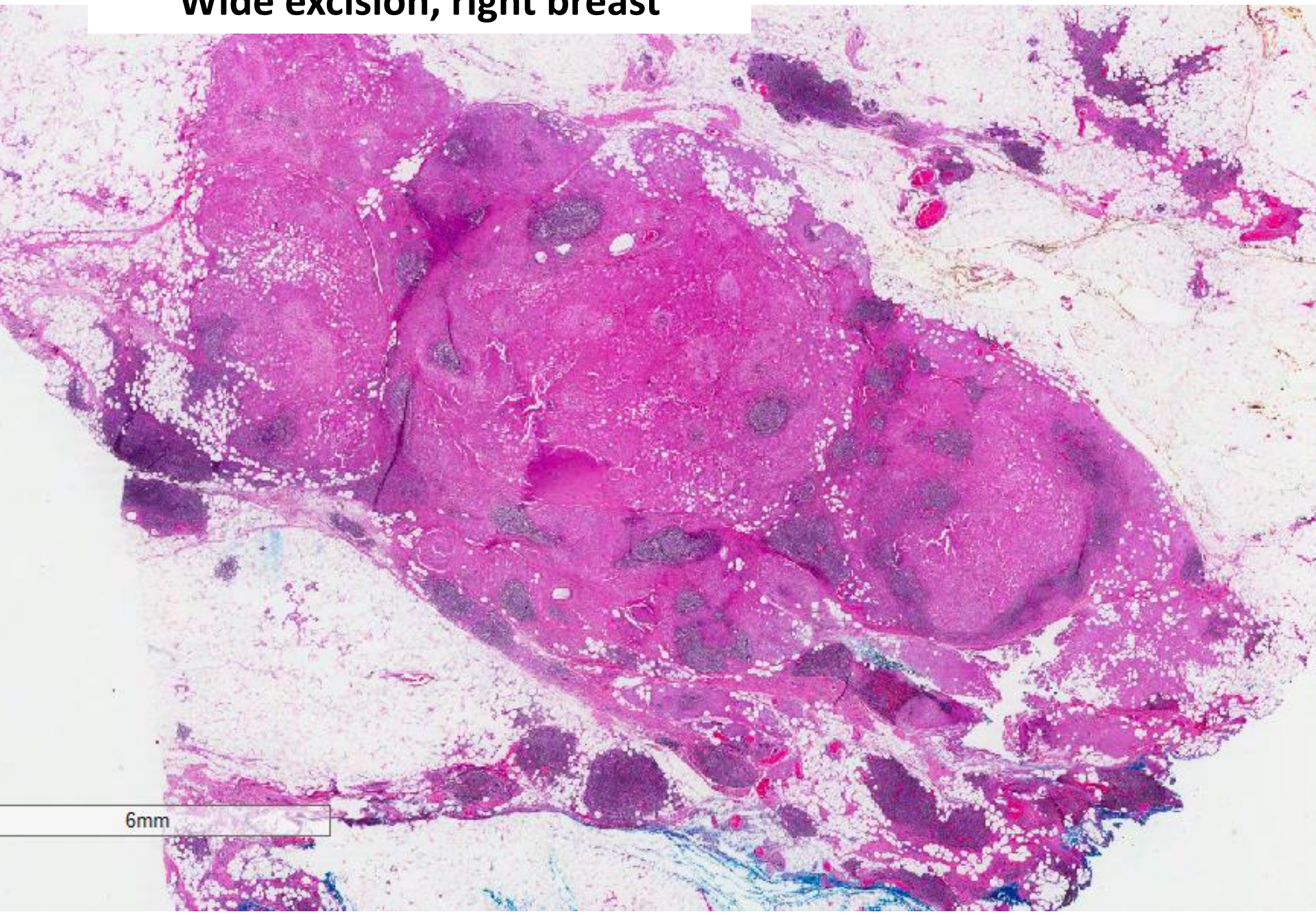
March 2010, right breast ultrasound

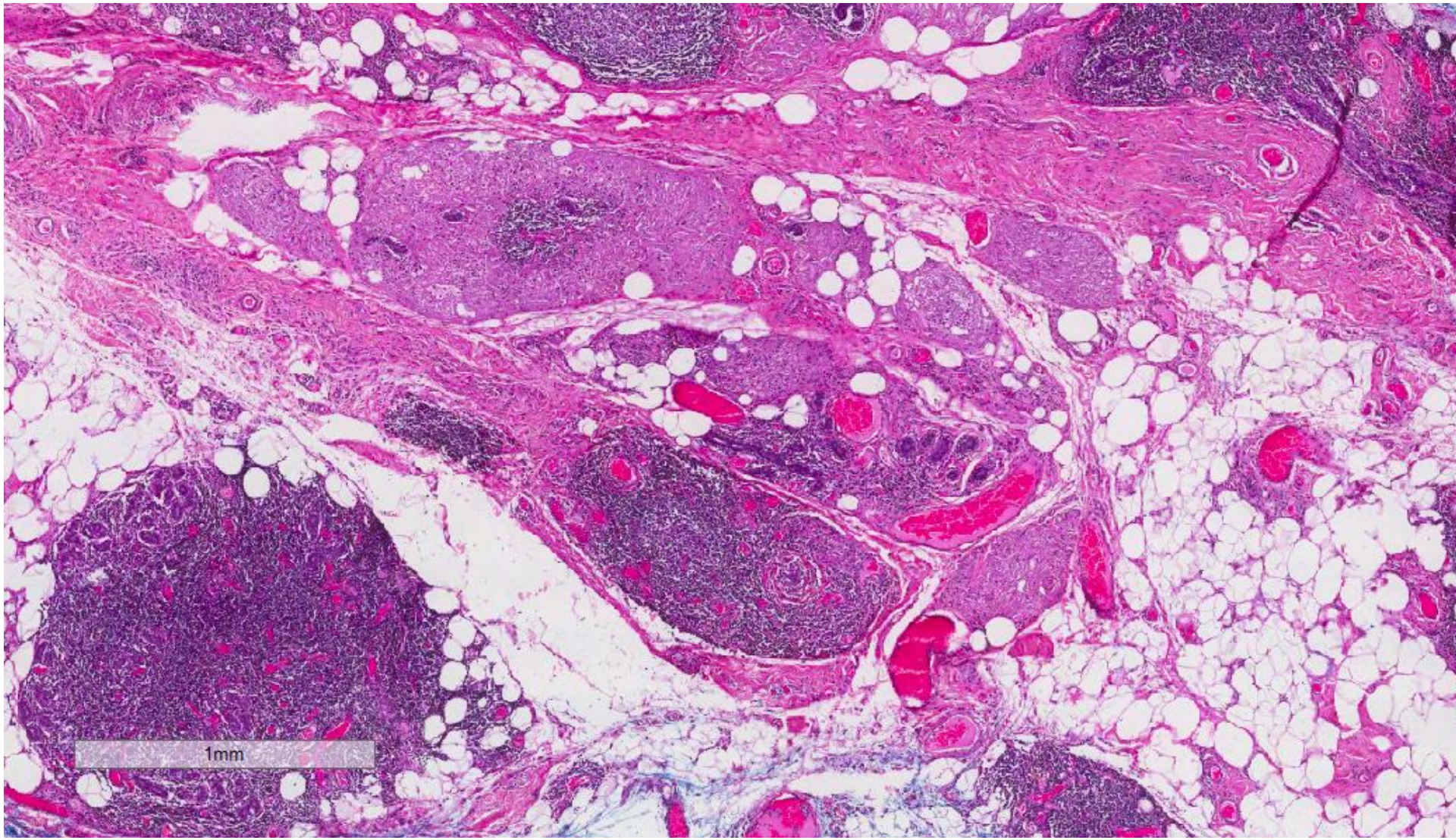


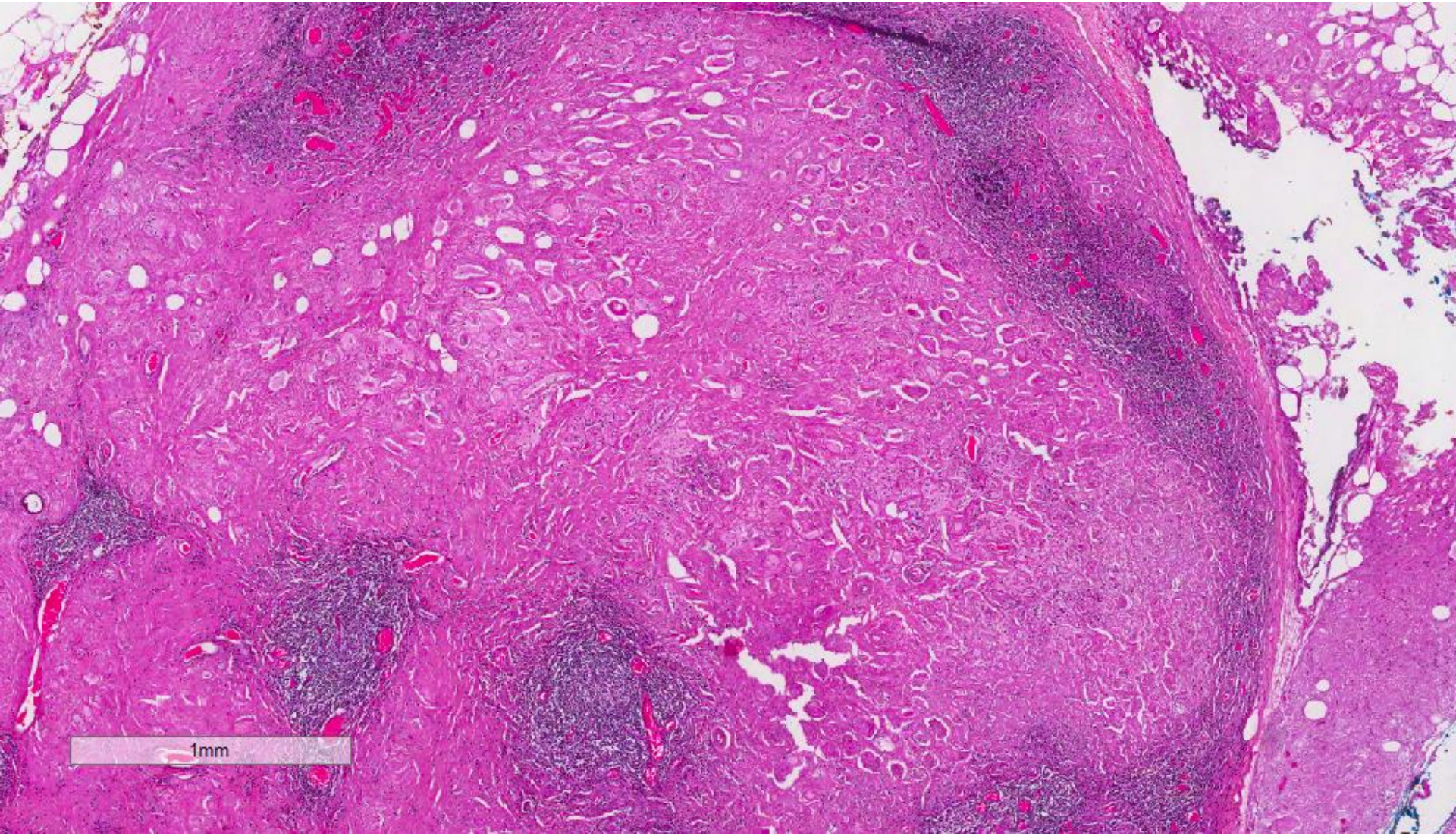
Wide excision, right breast

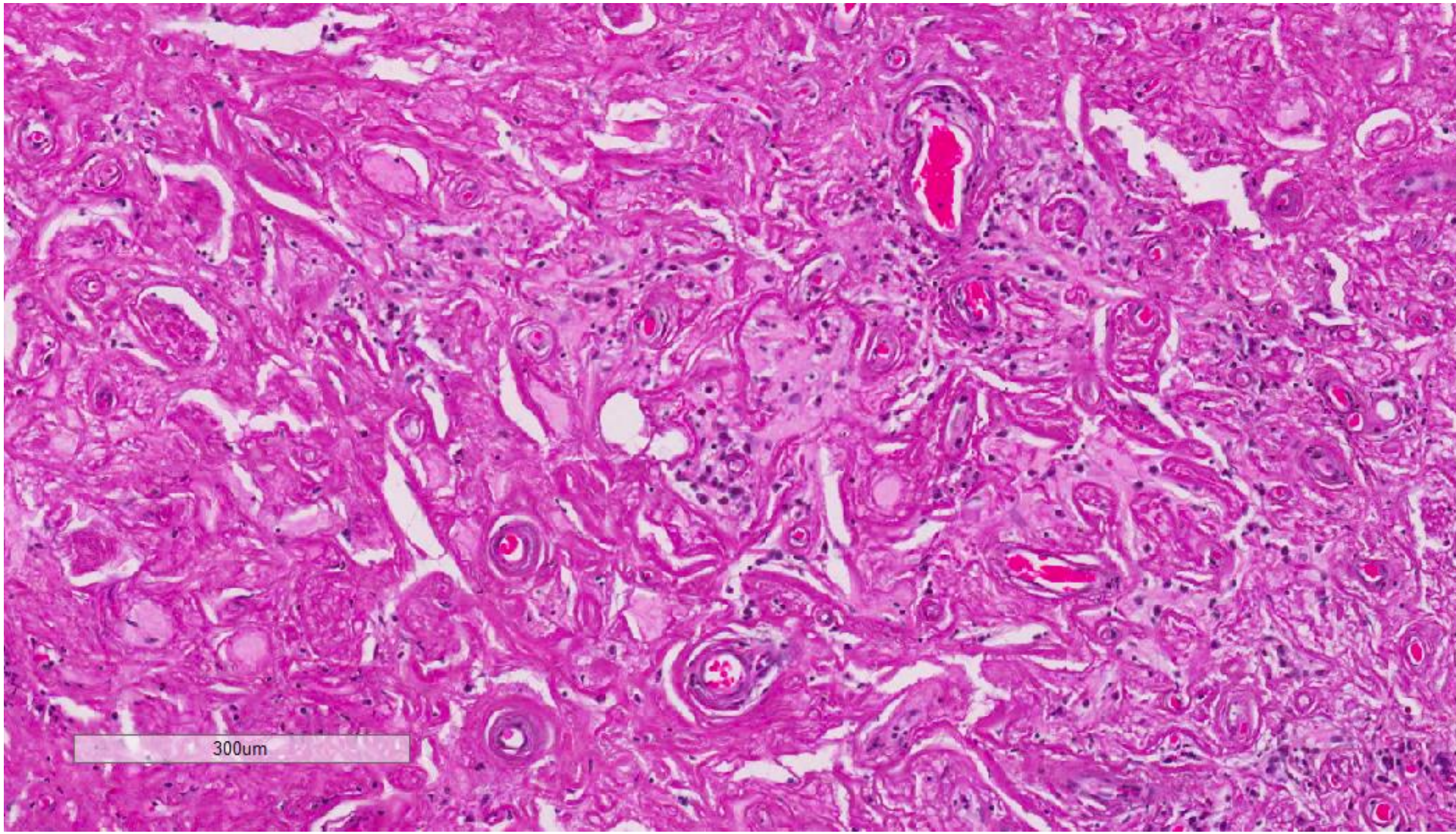


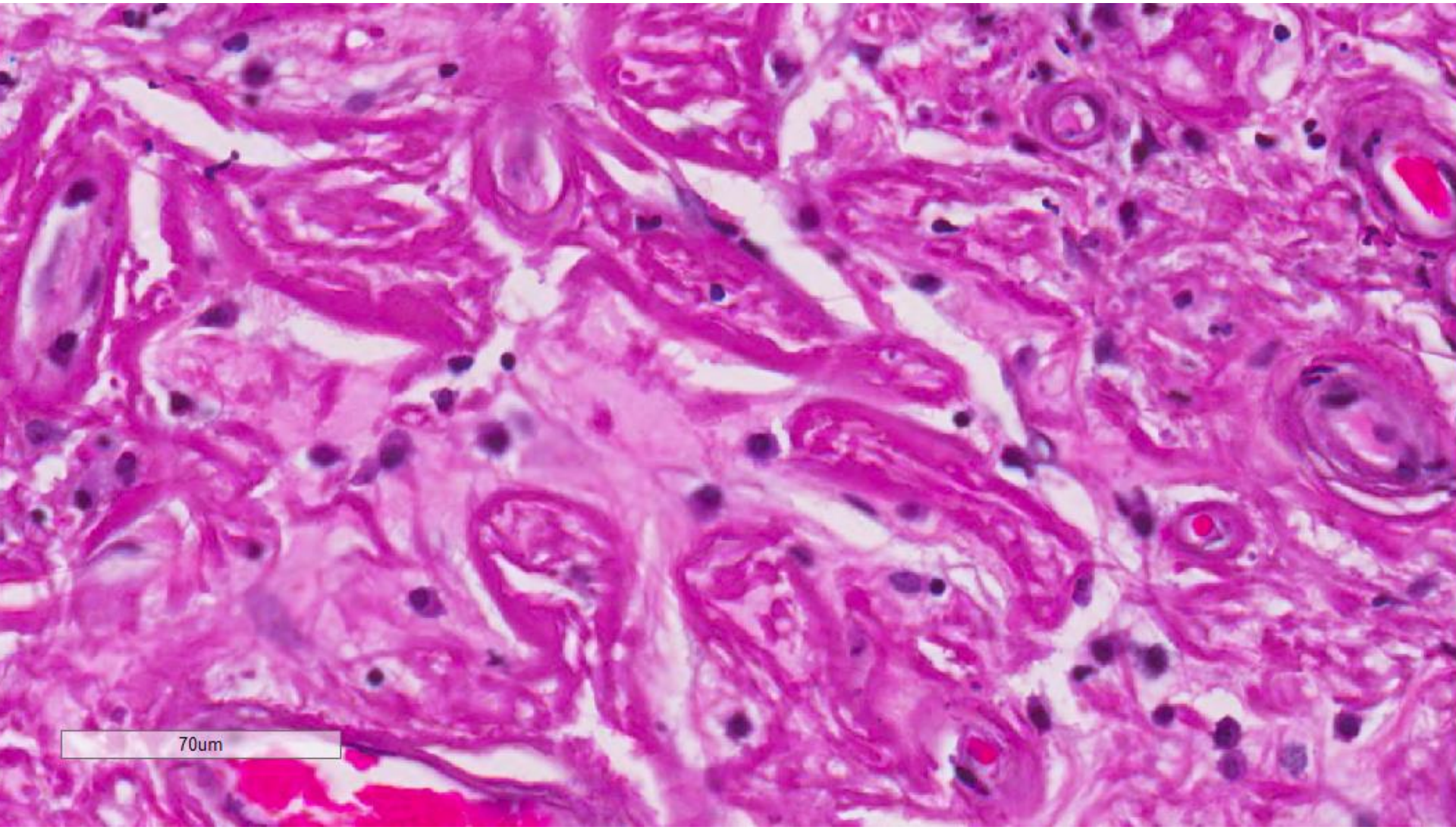
Wide excision, right breast

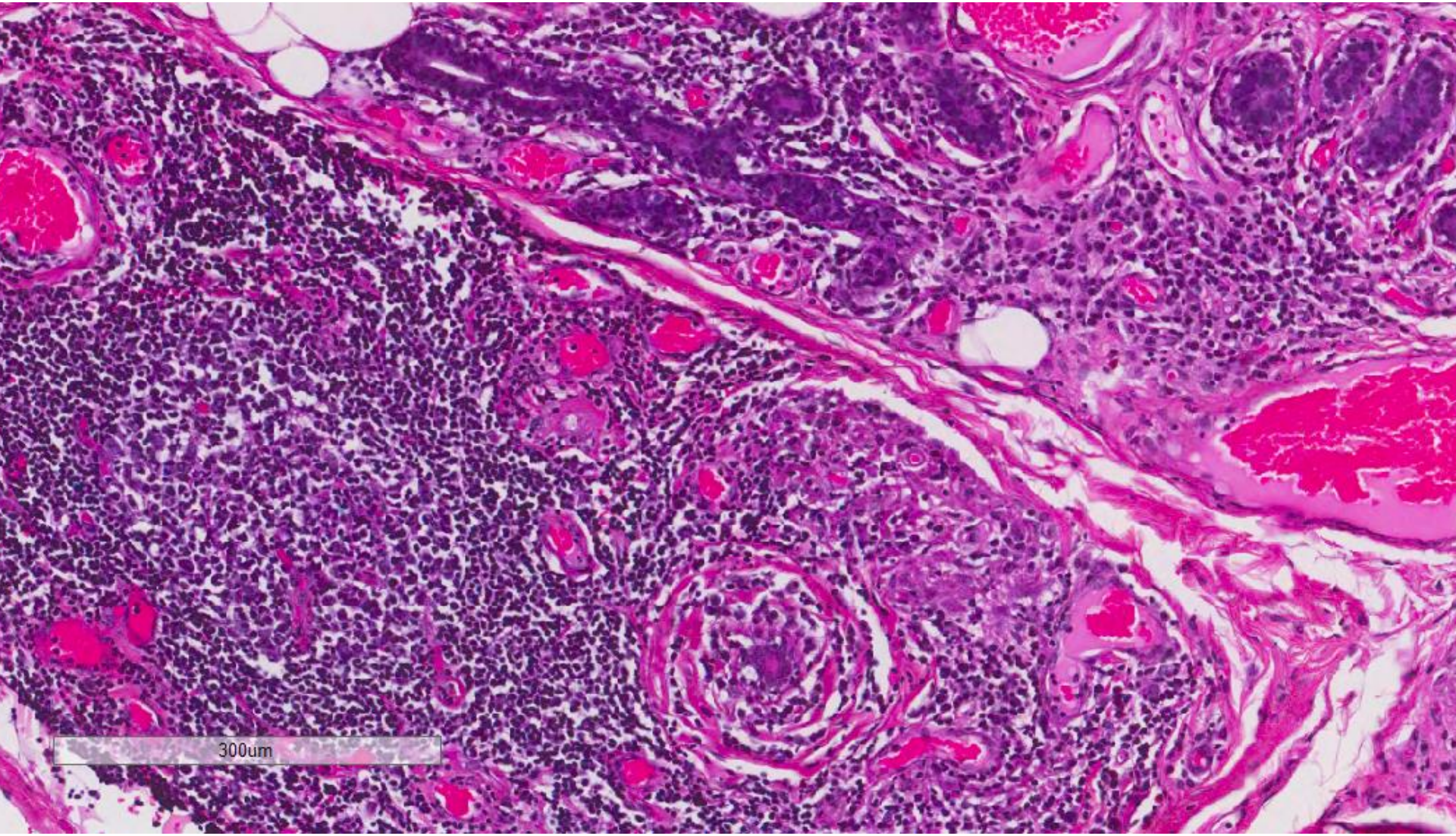



1mm


1mm


300um


70um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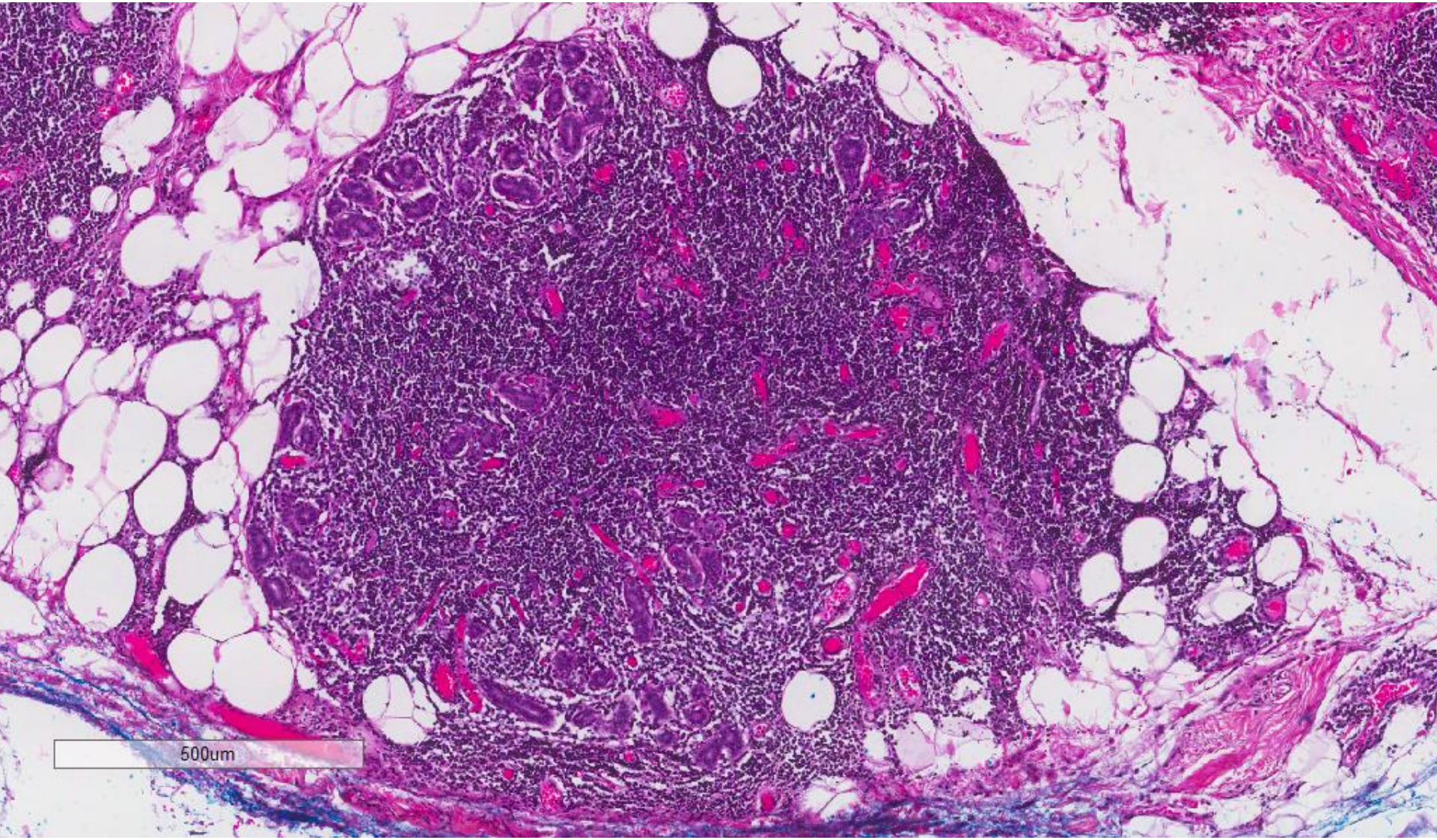
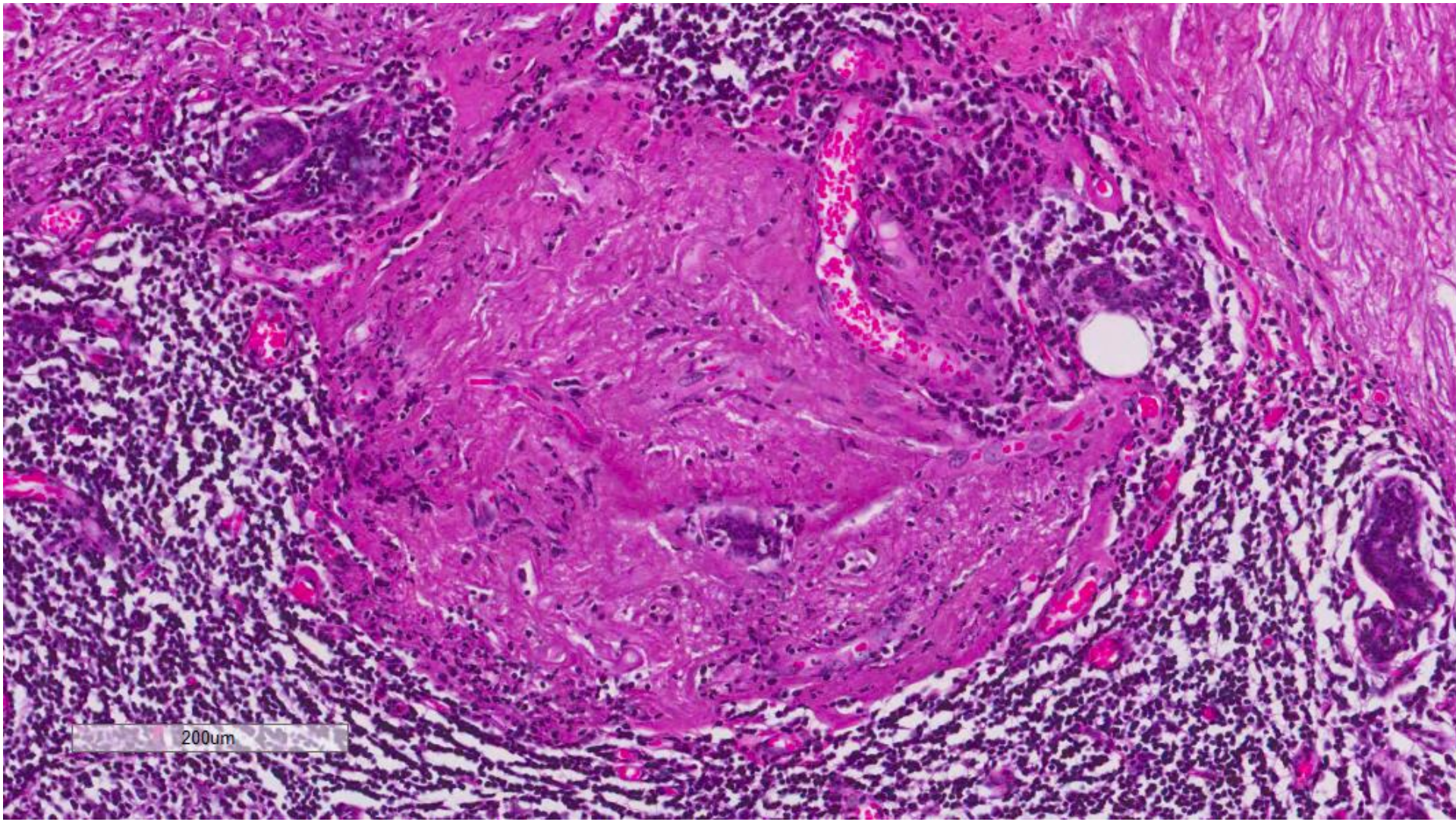
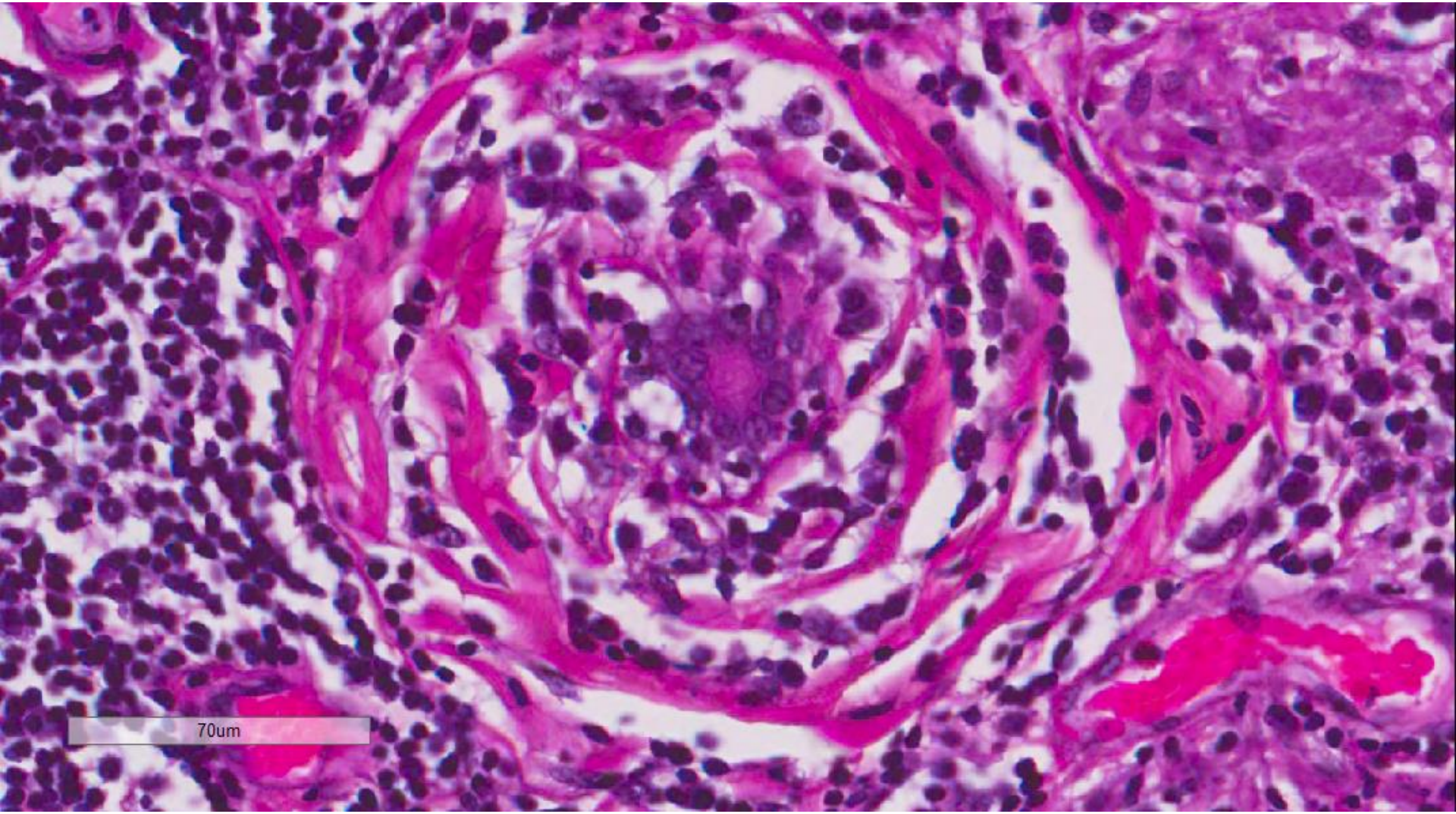

500um


200um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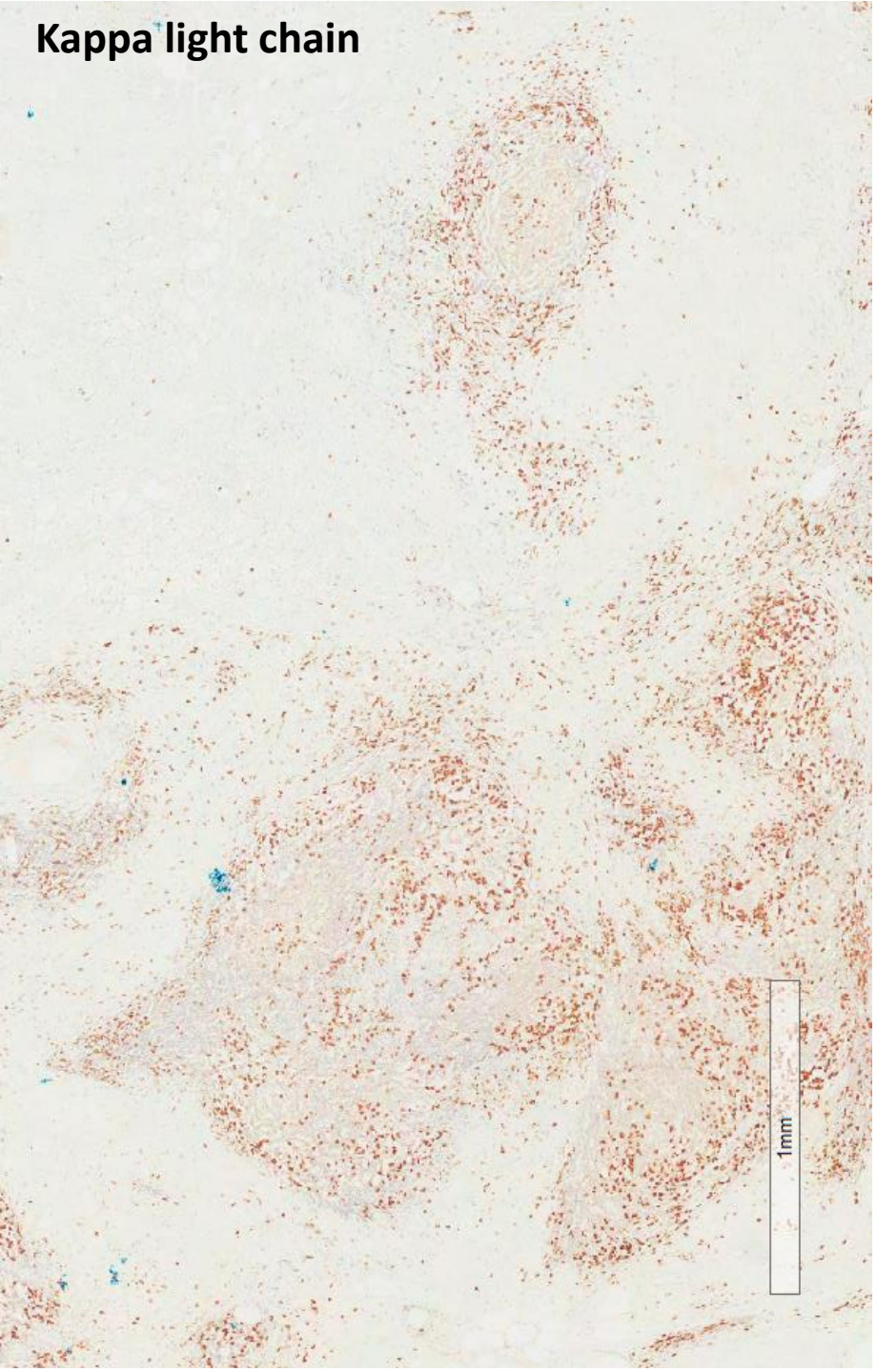
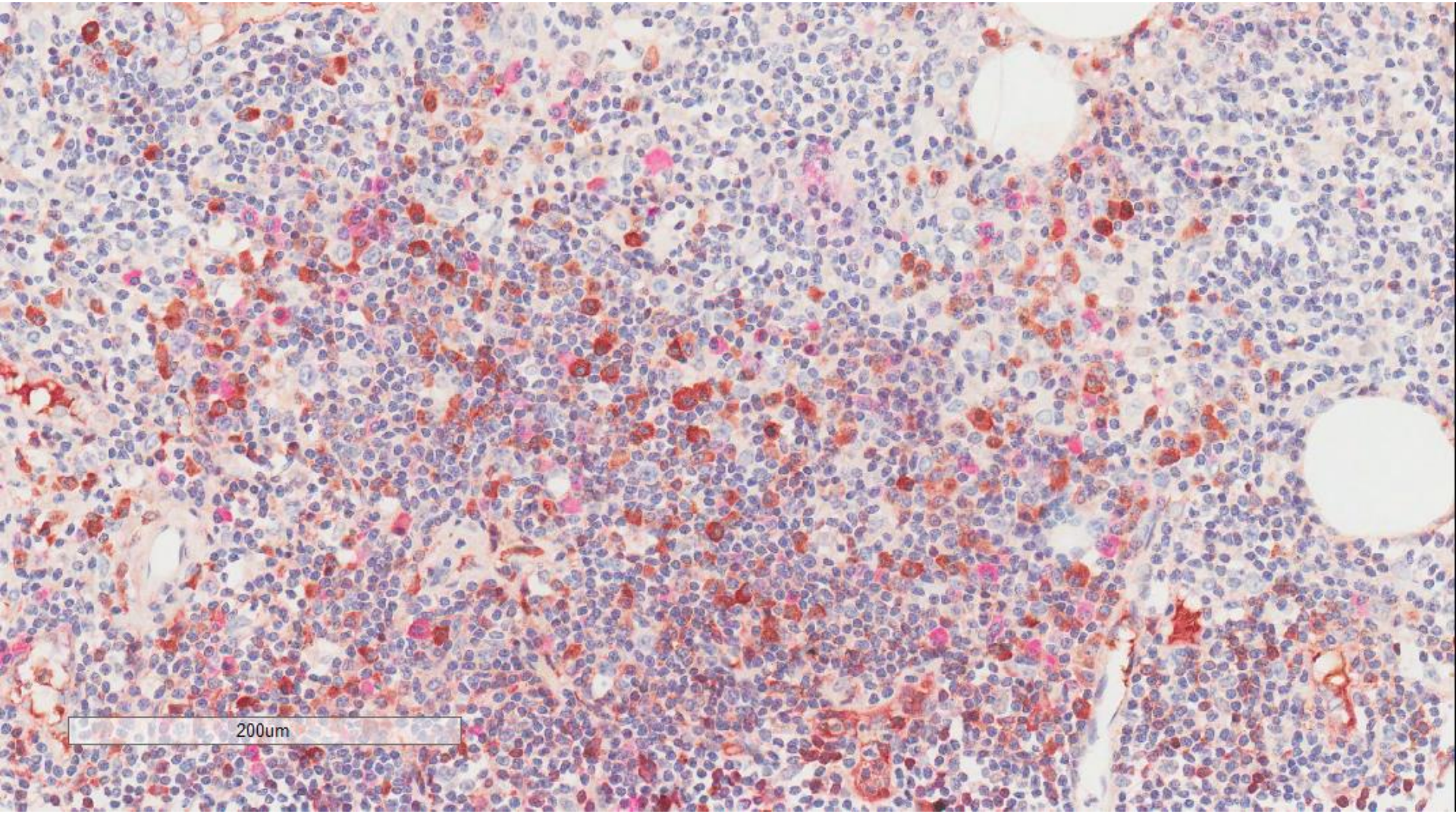
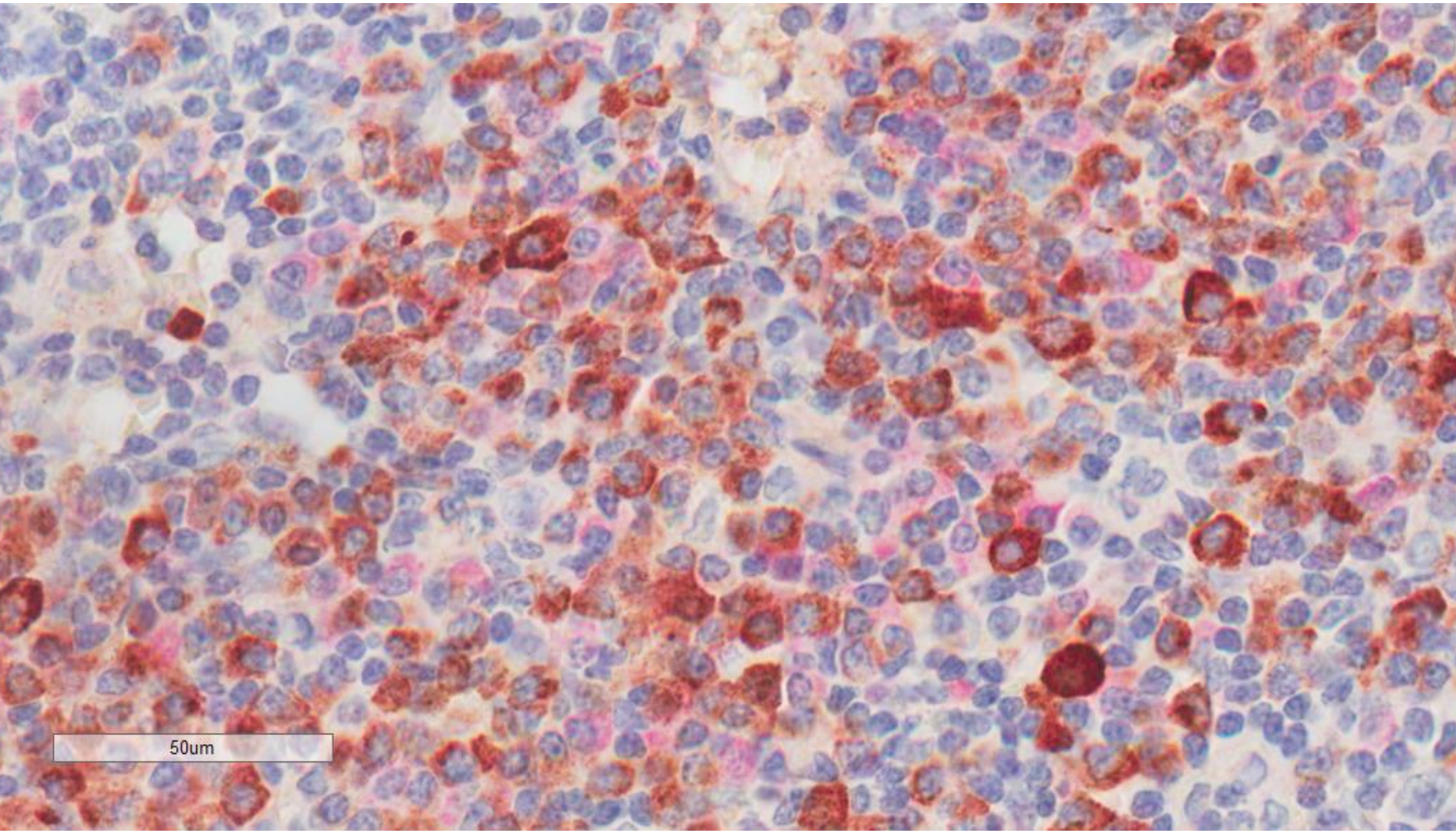

Kappa light chain
1mm


Lambda light chain
1mm

IgG4 (brown) /IgG (red)



IgG4 (brown) /IgG (red)



IgG4-related sclerosing disease

IgG4-related sclerosing mastitis

- Recently described as part of the IgG4-related sclerosing disease spectrum *{Cheuk et al. AJSP 2009 Jul;33(7):1058-64}*
  - 4 patients with IgG4-related sclerosing mastitis.
  - All females, mean age of 47.5 years.
  - Painless masses in 1 or both breasts.
  - One patient had concurrent IgG4-related lymphadenopathy, another had eyelid swelling of undetermined cause.
  - Serum IgG4 titre elevated in 1 tested patient.
  - Circulating autoantibodies found in 3 tested patients.
  - All patients were well with no recurrence after excision or biopsy of the mass.

IgG4-related sclerosing mastitis

- Histological features:
  - Dense lymphoplasmacytic infiltrates.
  - Prominent stromal sclerosis.
  - Loss of breast lobules.
  - Phlebitis in 1 case.
  - IgG4 cells ranged from 272 to 495 per high-power field, constituting 49% to 85% of all IgG cells.

  {IgG4 cells were scarce in 9 of 9 cases of lymphocytic mastitis and 6 of 7 cases of granulomatous mastitis studied as controls.}

IgG4-related sclerosing mastitis

- Appears to be a distinctive form of mastitis, sometimes accompanied by other components of IgG4-related sclerosing disease.
- Favourable clinical outcome.

IgG4-related sclerosing disease

- Elevated serum titre of IgG4.
- IgG4 is the least common (3% to 6%) of the 4 subclasses of IgG, & is a surrogate marker for the recently characterized IgG4-related sclerosing disease.
- Syndrome affects predominantly middle-aged and elderly patients, with male predominance.
- Involvement of 1 or more sites, usually in the form of mass lesions.
- Prototype is IgG4-related sclerosing pancreatitis (also known as autoimmune pancreatitis), most commonly presenting as painless obstructive jaundice with or without a pancreatic mass.

IgG4-related sclerosing disease

- Other common sites of involvement:
  - Hepatobiliary tract
  - Salivary gland
  - Orbit
  - Lymph node
  - Any organ-site can be affected, eg retroperitoneum, aorta, mediastinum, soft tissue, skin, central nervous system, breast, kidney, prostate, upper aerodigestive tract, and lung.
- Patients usually in good general condition, with no fever or constitutional symptoms.
- Laboratory results:
  - Raised serum globulin, IgG, IgG4, and IgE.
  - Lactate dehydrogenase is usually normal.
  - Low titres of autoantibodies (such as antinuclear antibodies and rheumatoid factor) can be present.
- Excellent response to steroid therapy.

IgG4-related sclerosing disease

- Natural history is the involvement of multiple sites with time, sometimes after many years.
- Disease can remain localized to 1 site in occasional patients.
- Pathologic findings:
  - Lymphoplasmacytic infiltrates
  - Lymphoid follicle formation
  - Sclerosis
  - Obliterative phlebitis
  - Atrophy and loss of the glands
  - 3 histologic patterns:
    - pseudolymphomatous, mixed, and sclerosing.
  - Increased IgG4+ cells in the involved tissues (>50 per high-power field, with IgG4/IgG ratio >40%)

IgG4-related lymphadenopathy

- Pathology of lymph nodes:
  - Multicentric Castleman disease-like features
  - Reactive follicular hyperplasia
  - Interfollicular expansion
  - Progressive transformation of germinal centers.
  - Unifying feature of increased IgG4+ plasma cells on immunostaining
- Nature and pathogenesis of IgG4-related sclerosing disease still uncertain.
- Occasional complication of development of malignant lymphoma and possibly carcinoma.

TABLE 4. Morphologic Spectrum of IgG4-related Sclerosing Disease in Extranodal Sites

	Pseudolymphomatous Pattern	Mixed Pattern	Sclerosing Pattern
Lymphoid component	Prominent and dense infiltrate of lymphocytes and plasma cells, often accompanied by interspersed reactive lymphoid follicles	Moderately prominent lymphoplasmacytic infiltrates, often accompanied by scattered reactive lymphoid follicles	Patchy aggregates of lymphocytes and plasma cells, with or without lymphoid follicle formation
Sclerosis	Relatively minor	Obvious, taking the form of broad bands and delicate strands	Sclerotic tissue constitutes the major bulk of the lesion
Phlebitis	Phlebitis uncommonly seen	Variable	Obliterative phlebitis commonly found
Borders of lesion	Circumscribed or ill-defined	Circumscribed or ill-defined	Ill-defined
Sites of disease commonly exhibiting the morphologic pattern	Lacrimal gland, salivary gland, breast, skin	Miscellaneous sites	Retroperitoneum (retroperitoneal fibrosis); mediastinum (mediastinal fibrosis); orbit (orbital inflammatory fibrosclerosing lesion)

Cheuk & Chan, Adv Anat Pathol 2010;17:303–332

TABLE 11. Clues to Diagnosis of IgG4-related Sclerosing Disease

The possibility of IgG4-related sclerosing disease should be seriously considered in the following scenarios, especially if there is evidence of concomitant or history of pancreatic, lacrimal gland, or salivary gland lesions.

Extranodal sites:

- Unexplained abundance of mature plasma cells
- Morphologic features of pseudolymphoma
- Morphologic features of inflammatory fibrosclerosing lesion
- Morphologic features of "inflammatory pseudotumor" with many plasma cells and no significant population of myofibroblasts

Lymph node:

- Morphologic features suggestive of multicentric Castleman disease in a patient with otherwise good general condition
- Atypical lymphoid hyperplasia rich in plasma cells
- Morphologic features reminiscent but falling short of angioimmunoblastic T-cell lymphoma in a patient with good general condition and normal or marginally raised serum lactate dehydrogenase level

Cheuk & Chan, Adv Anat Pathol 2010;17:303–332

TABLE 9. Histologic Criteria of IgG4-related Sclerosing Disease

All of the following criteria have to be satisfied:

(1) Compatible morphology:

Extranodal sites*

(a) Lymphoplasmacytic infiltration ± lymphoid follicles

(b) Sclerosis

(c) ± Phlebitis; arteries always spared except in the lung

(d) No significant population of proliferated myofibroblasts

Lymph node

(a) Increased plasma cells

(b) Usual reactive lymphoid follicles ± hyaline-vascular follicles, or interfollicular expansion with increased activated lymphoid cells

(2) Absolute number of IgG4+ cells > 50/HPF†

(3) Percentage of IgG4+/IgG+ cells > 40%†

*Not all features may be present in small biopsies.

†For enumeration of $IgG4^+$ or IgG^+ cells, select areas with the highest density of positive cells. Three high-power fields (HPF) are counted, and an average number of positive cells per HPF is calculated. One HPF covers an area of 0.196 mm^2 (× 40 objective, × 10 eyepiece, 20 mm field of view).

Cheuk & Chan, Adv Anat Pathol 2010;17:303–332

Follow-up

- Uneventful.
- No serologies performed.
- Screening mammography 3 years later disclosed a new lesion in the left breast (case 42).

Breast Pathology Course 2014