
The Multifaceted Pathologies of Cardiac Allograft Vasculopathy

Gregory A. Fishbein, M.D.

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David Geffen
School of Medicine

UCLA Health

Disclosures

- I have nothing to disclose.



Cardiac Allograft Vasculopathy (CAV)

- A.k.a. transplant atherosclerosis, transplant coronary artery disease (TCAD), graft arteriosclerosis, etc...
- The primary factor limiting long-term graft survival in both adults and children^{1,2}
- The dominant indication for **retransplantation** after 1 year³
- One of the major causes of **death** at ≥ 3 years following transplantation³



What is CAV?

- ISHLT 2010 consensus statement defines CAV as an “intimal proliferation”
- Proposes a three-tiered grading system
 - ISHLT CAV1 - mild
 - ISHLT CAV2 - moderate
 - ISHLT CAV3 - severe
- System is based on angiographic assessment and cardiac function, not pathologic evaluation



What is CAV?

ISHLT 2010 Consensus Statement

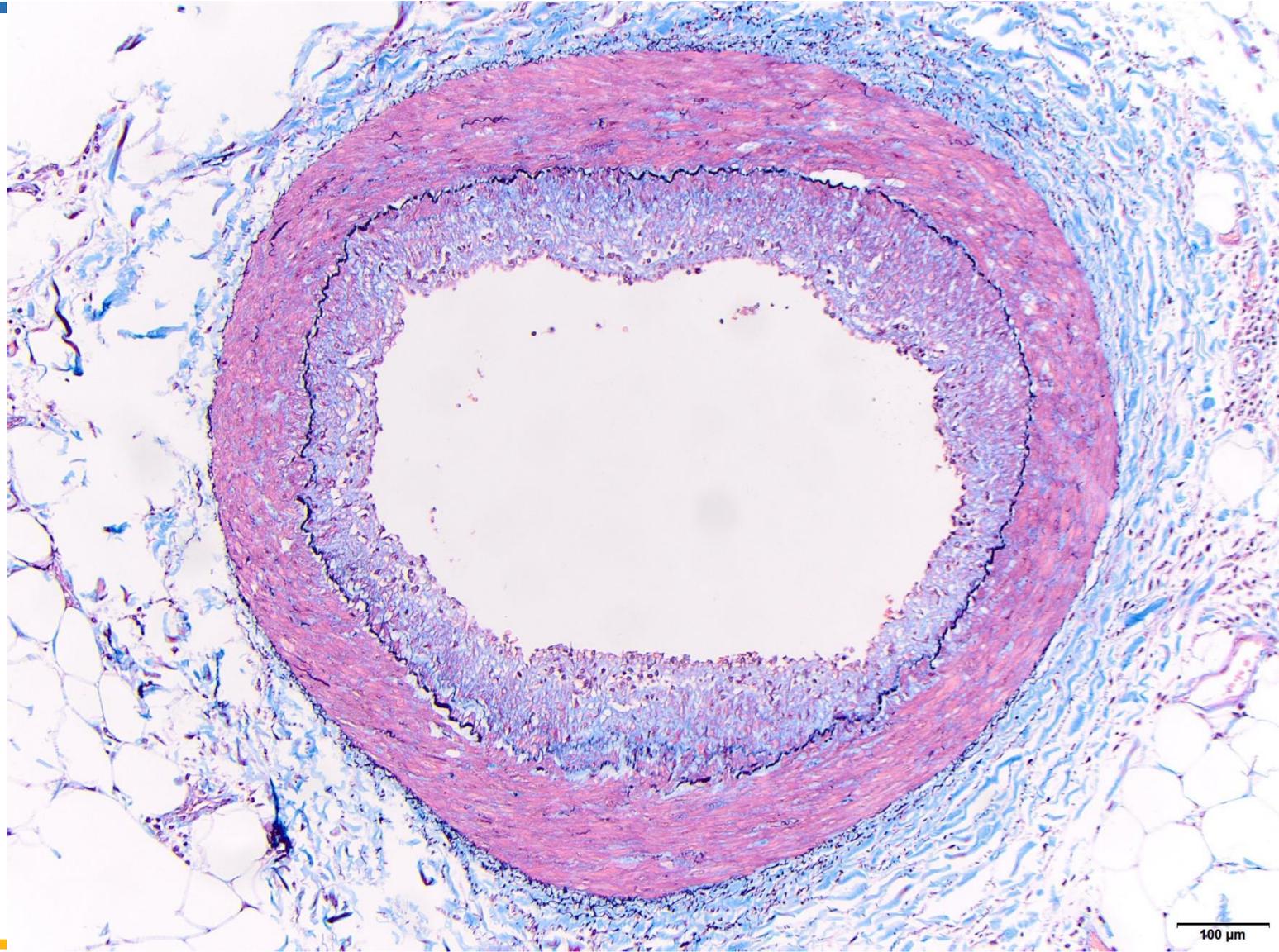
Table 1 Unanswered Questions in Cardiac Allograft Vasculopathy

- What is significant angiographic cardiac allograft vasculopathy?
- How does allograft function play a role in the nomenclature for defining severity?
- Is there a “histopathologic” definition of cardiac allograft vasculopathy?
- How does intravascular ultrasound fit into the current diagnostic schema?
- What is the value of new non-invasive tests and gene-based or protein-based biomarkers?



“Classic” CAV

- Intimal fibromuscular proliferation
- Concentric thickening
- Sparse chronic inflammation
- Epicardial and intramyocardial



Trichrome/EVG



The Three Pathologies of CAV

- Atherosclerosis
- Vascular inflammation
- Fibromuscular intimal hyperplasia



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- Atherosclerosis
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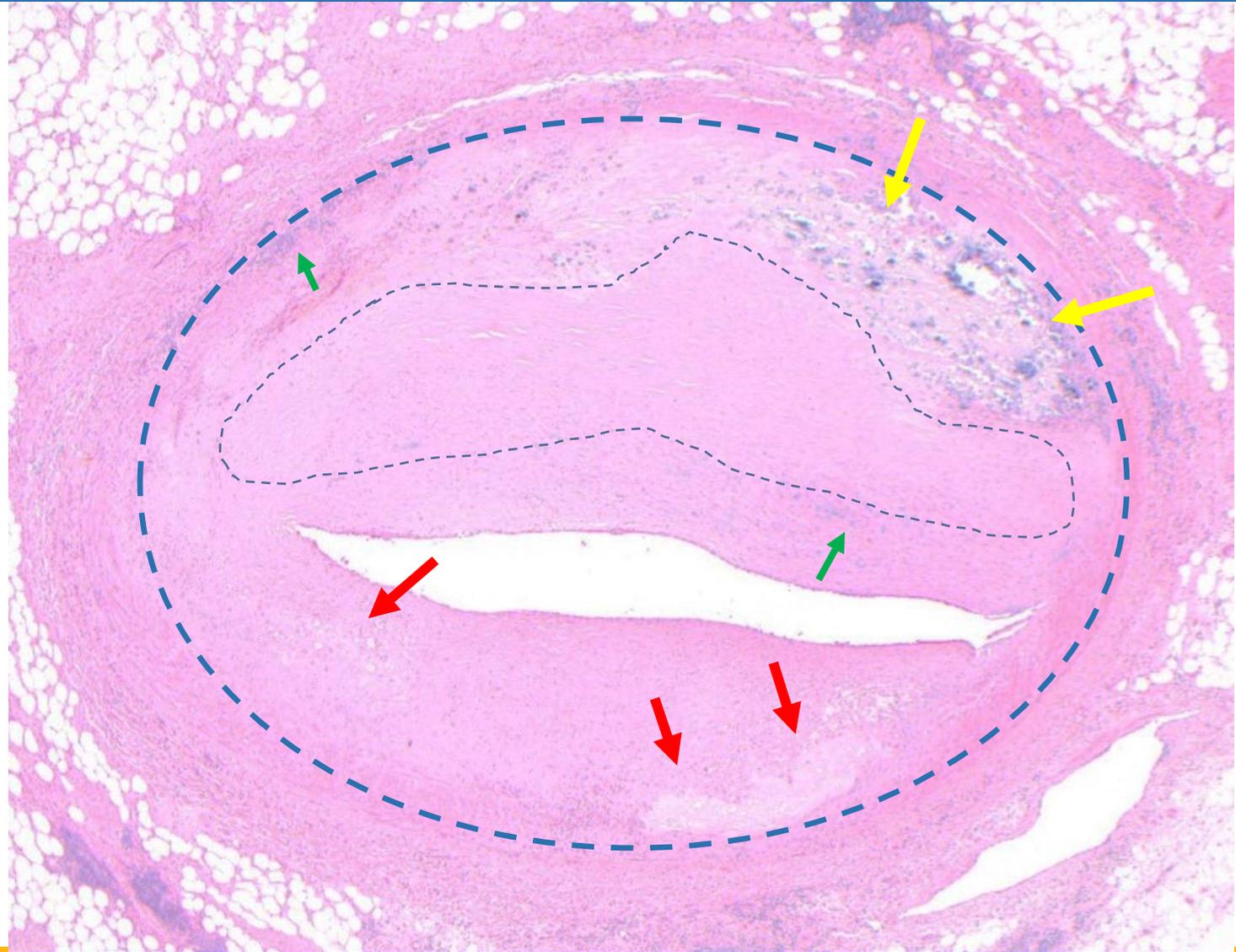
Atherosclerosis

- “Arteriosclerosis with atheromatosis”
 - Rabson SM. *Am J Clin Pathol.* 1954;24: 472.
- A disease of the elastic and large muscular arteries in which the ***atheroma*** is the characteristic lesion
 - Lipids
 - Connective tissues
 - Inflammatory cells
 - Extracellular components (e.g. matrix proteins, enzymes, Ca²⁺)

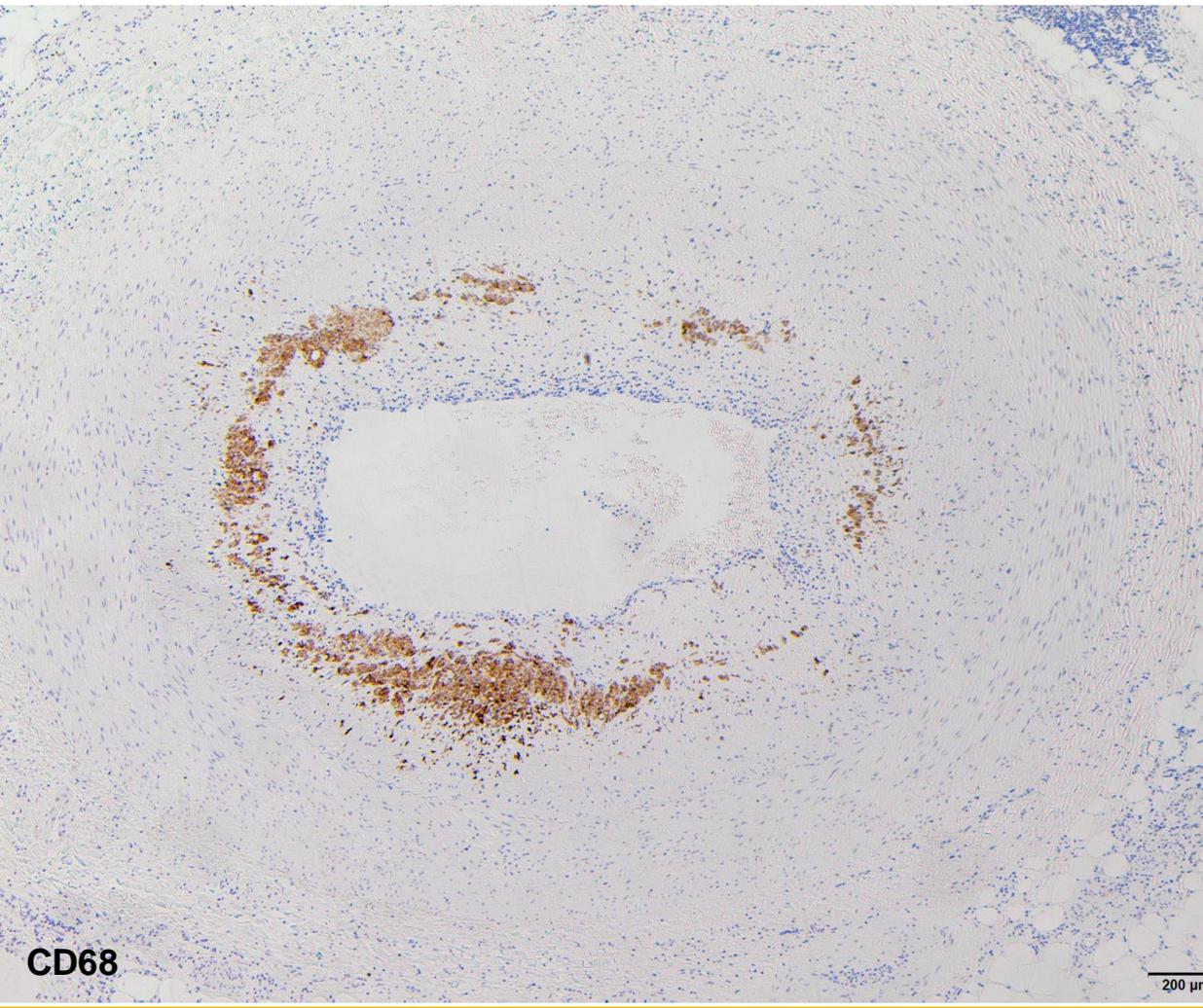
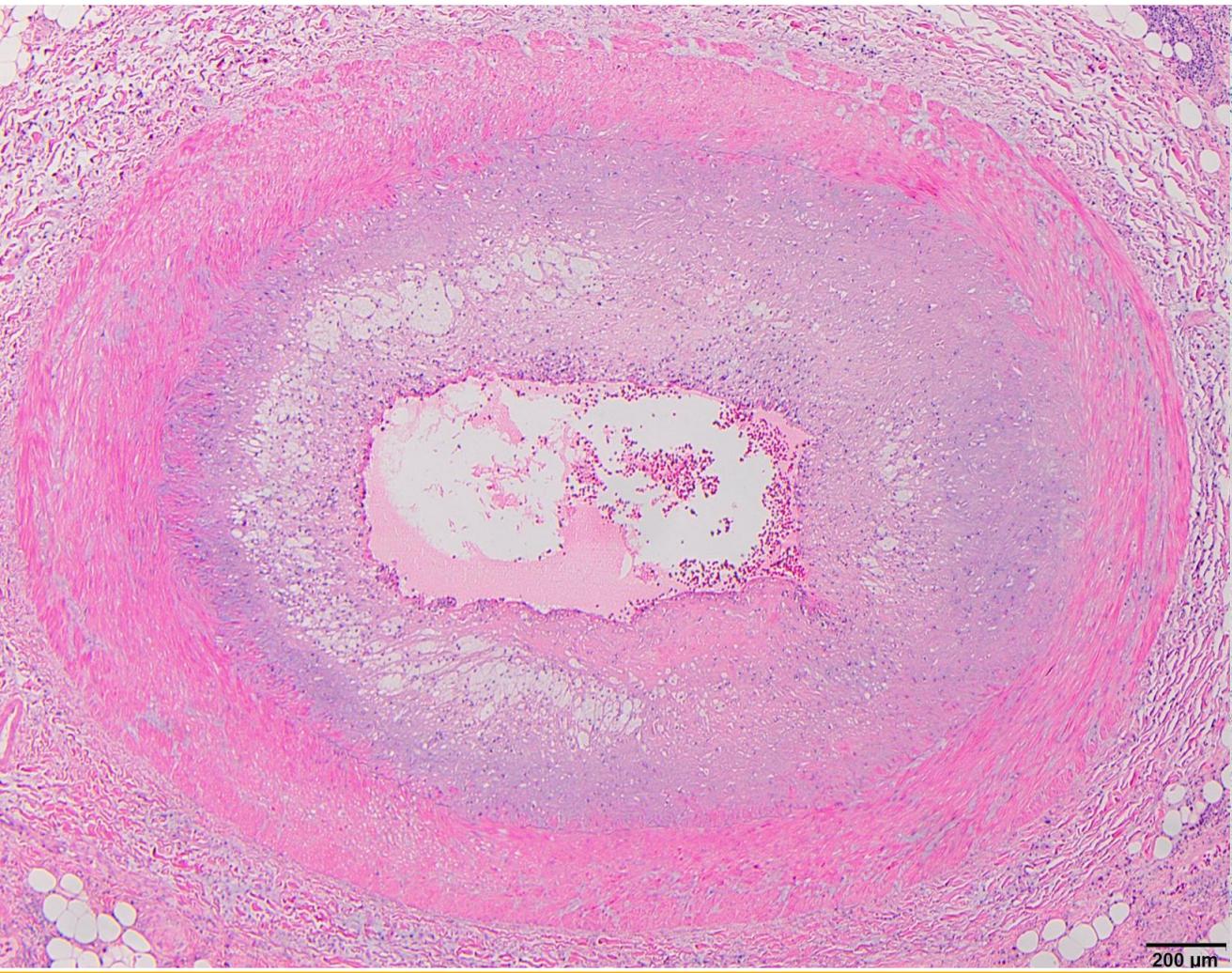


Atherosclerosis

- Intimal proliferation
- Lipids
- Inflammation
- Connective tissues
- Extracellular components (e.g. Ca^{2+})



16-year-old girl



CD68



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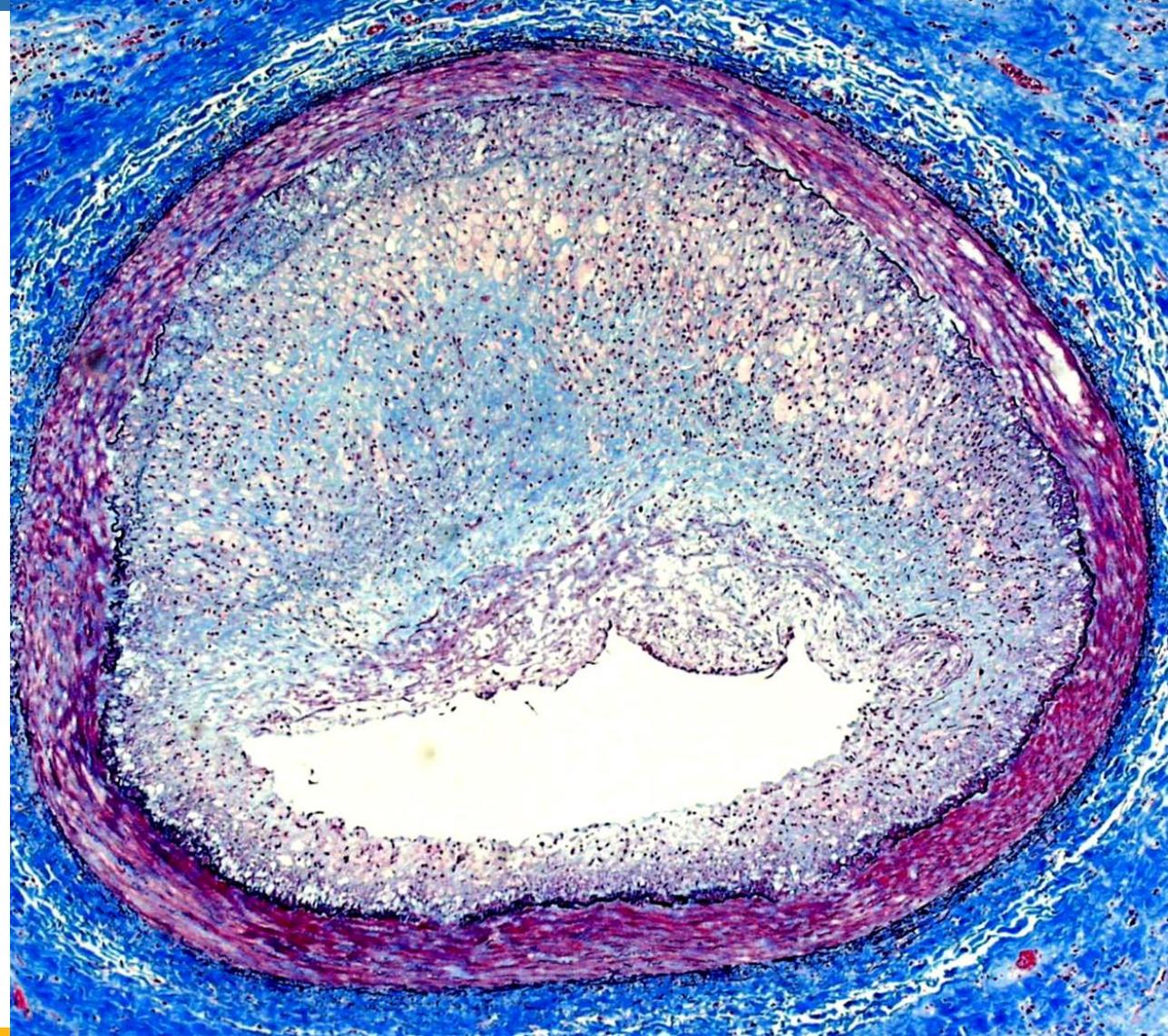
“Transplant Atherosclerosis”

- A historic and problematic term
- Accelerated atherosclerosis is part of CAV
 - As evidenced by pediatric cases
- Not all the lesions of CAV are atherosclerotic



Atherosclerosis

- Epicardial coronary arteries
- Strictly arterial
- A process of the intima
- Eccentric thickening
- A disease of adults



Trichrome/EVG



Atherosclerosis

- Epicardial coronary arteries
- Strictly arterial
- A process of the intima
- Eccentric thickening
- A disease of adults

CAV

- Epicardial and intramyocardial vessels
- Affects all types of vessels
- Can affect all layers
- Concentric thickening
- Adults and pediatric



The Three Pathologies of CAV

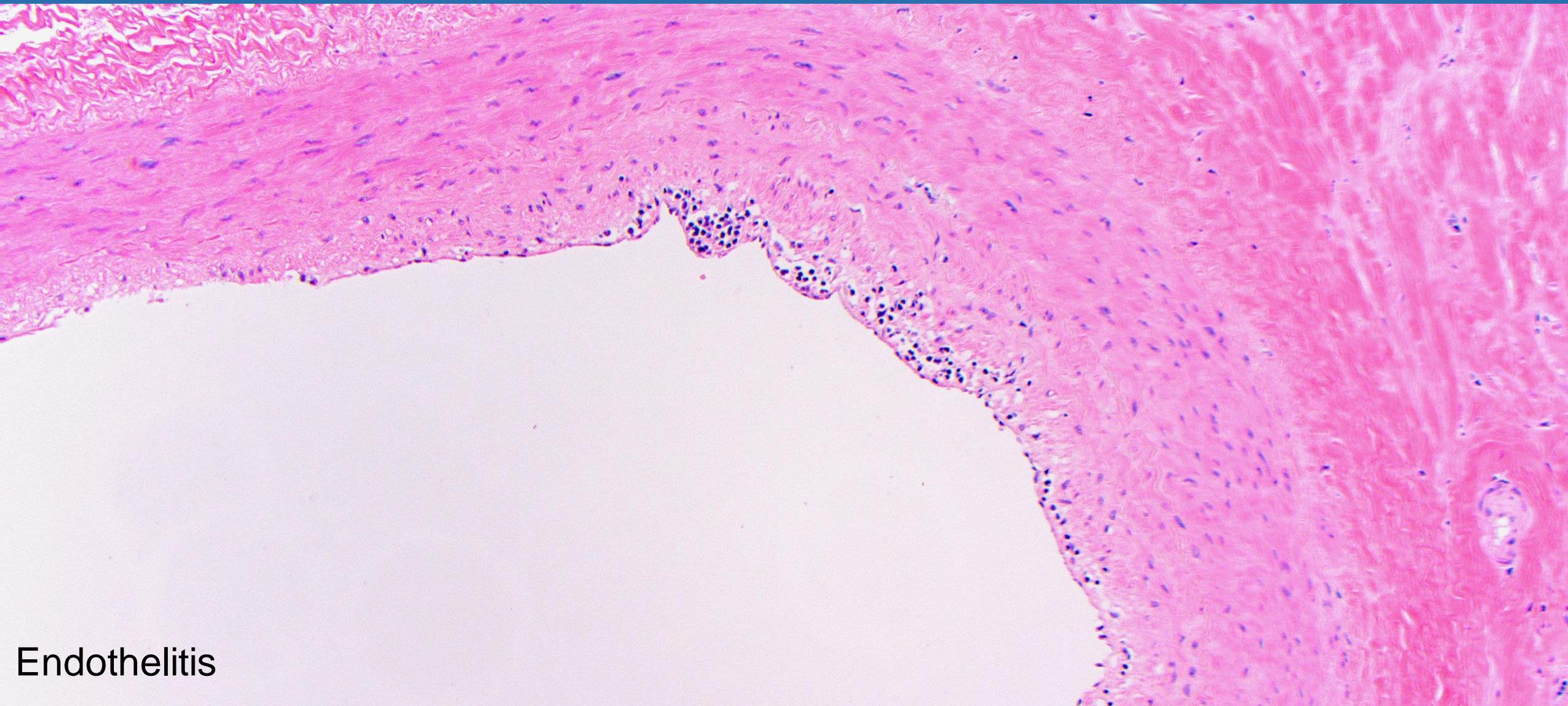
- Atherosclerosis
- **Vascular inflammation**
- Fibromuscular intimal hyperplasia



The Spectrum of Vascular Inflammation in CAV

- No inflammation at all
- Atherosclerosis
- Vasculitis
 - Endothelitis
 - (or endothelialitis, endotheliitis, etc...)
 - Full-thickness necrotizing vasculitis

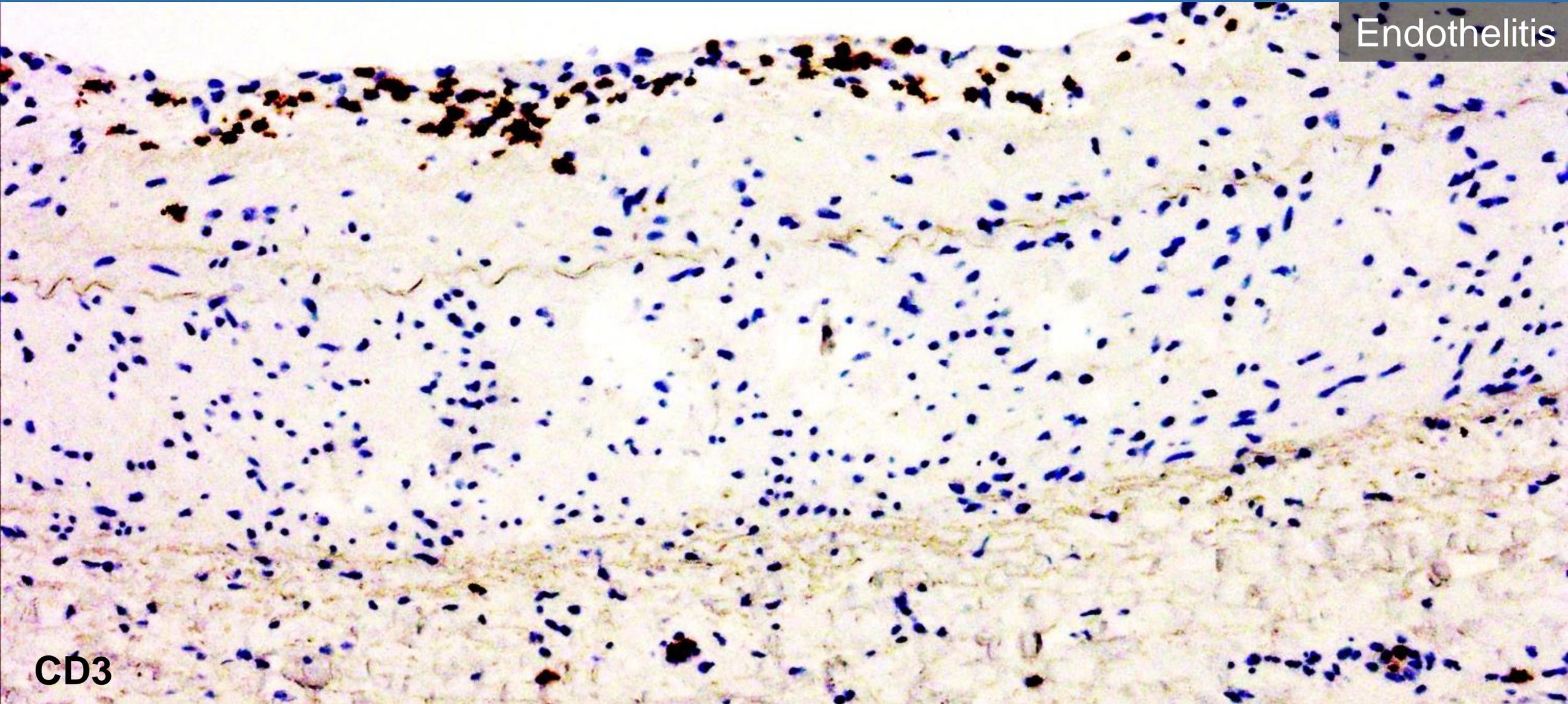




Endothelitis



Endothelitis

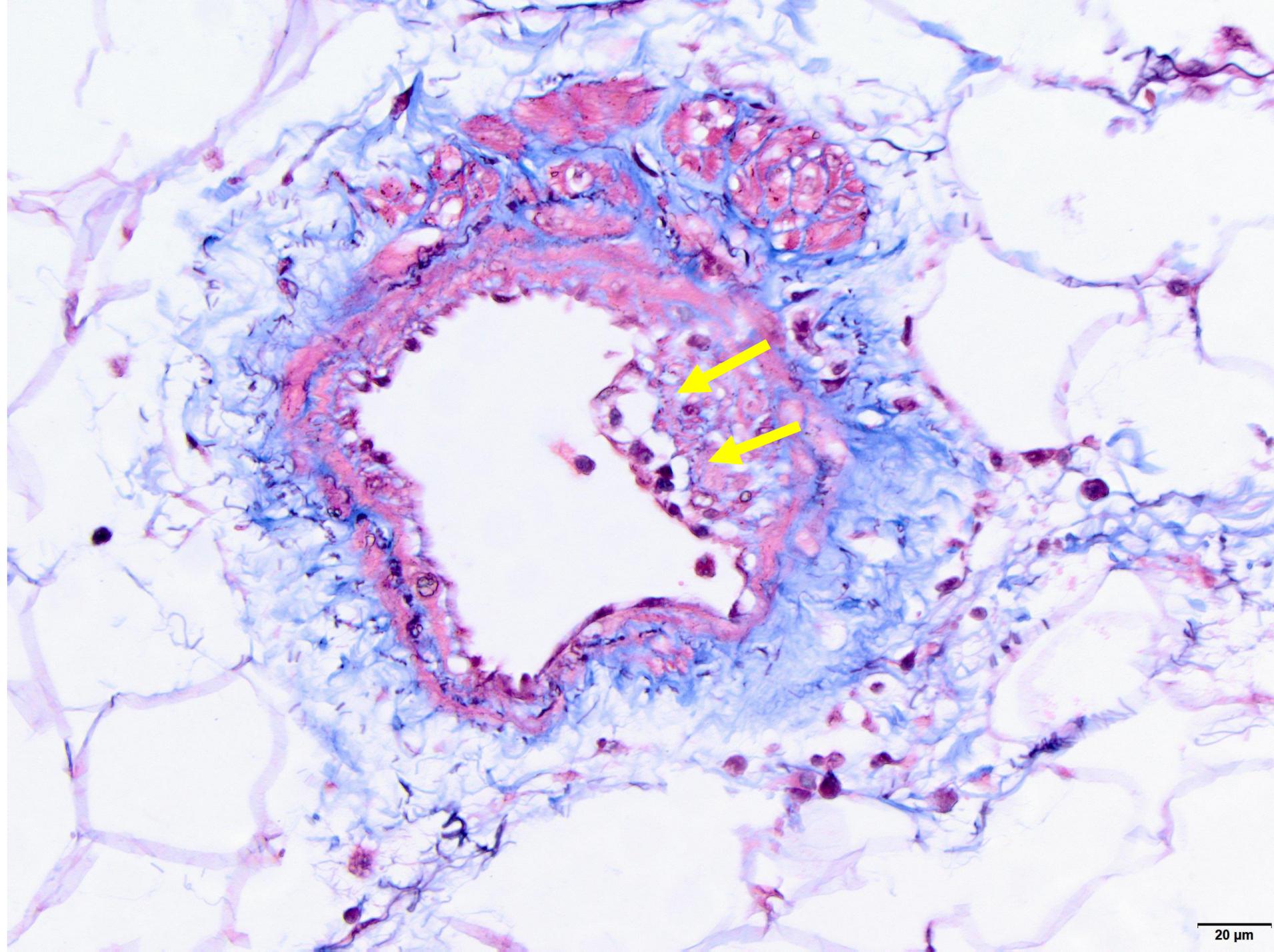


CD3



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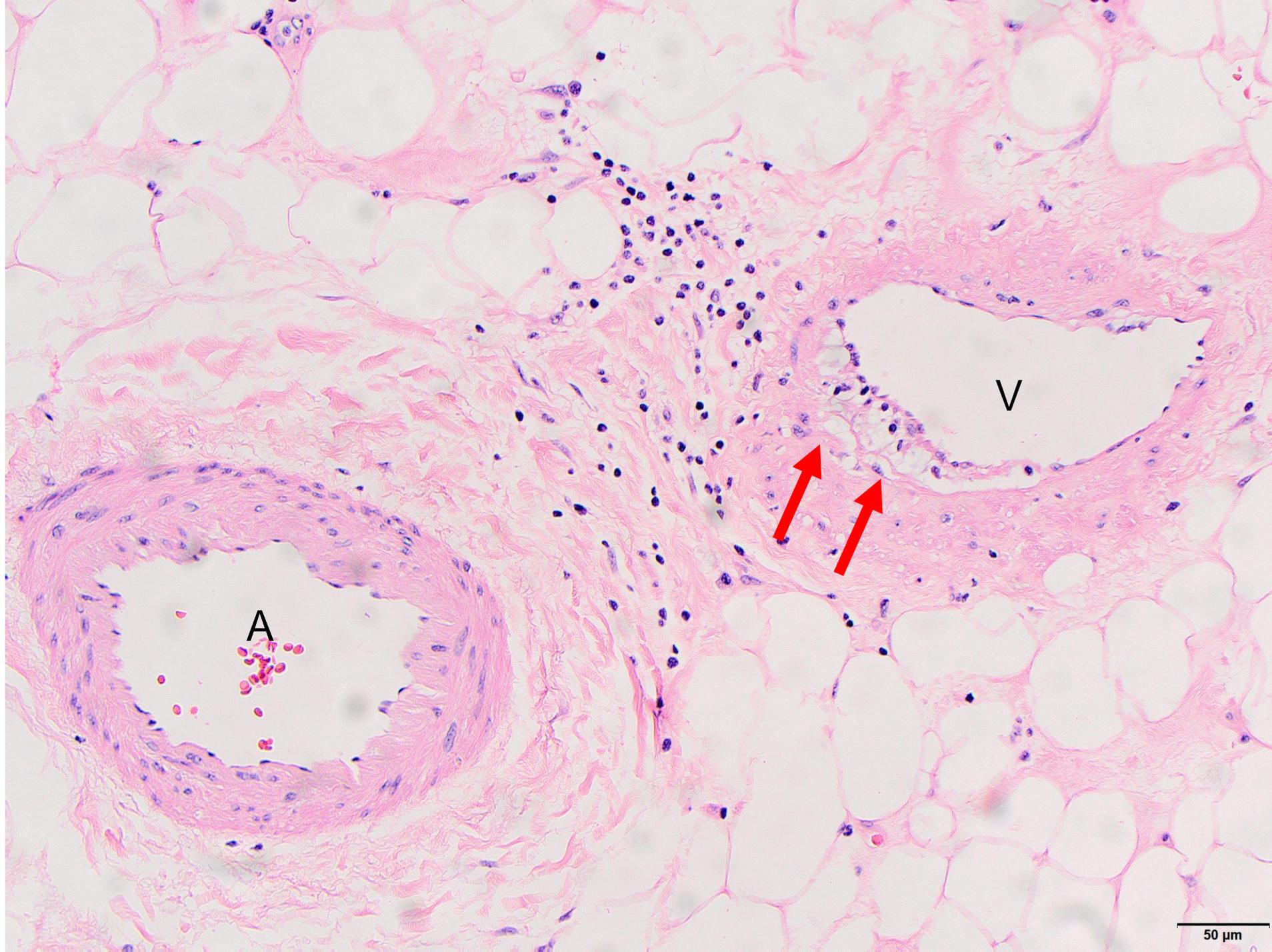
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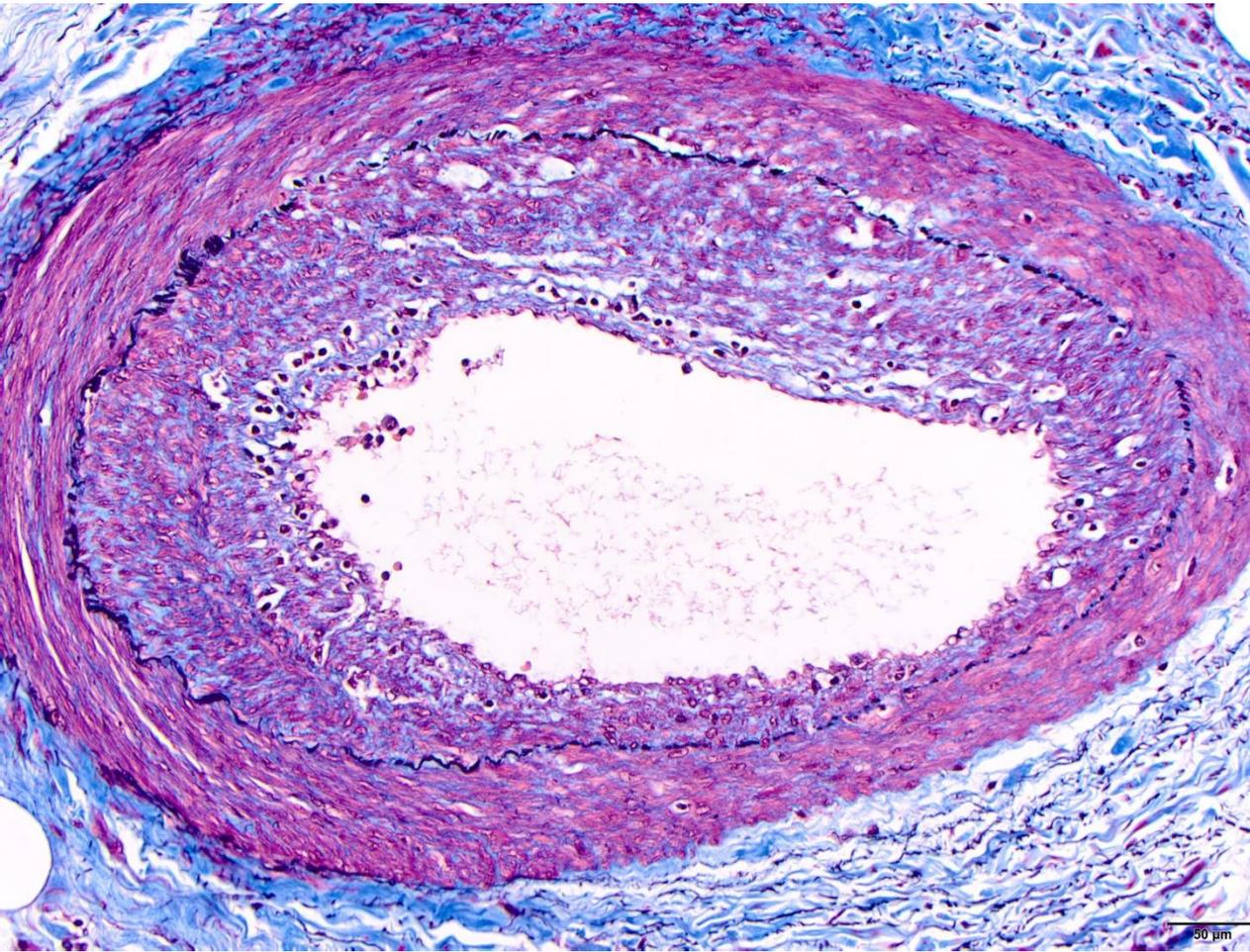
Arteriole with
endothelitis

Trichrome/EVG

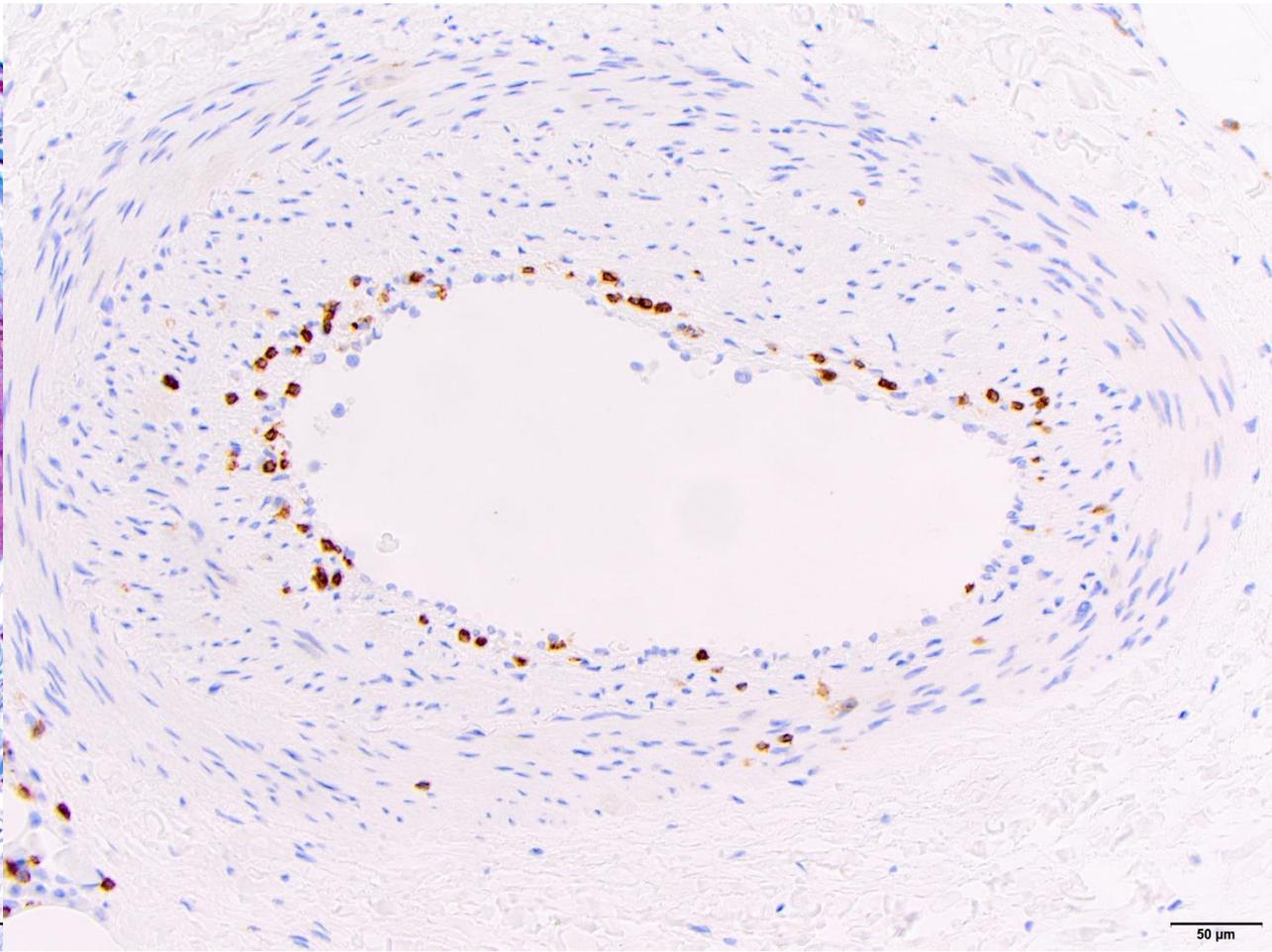
20 μ m



Vein with
endothelitis

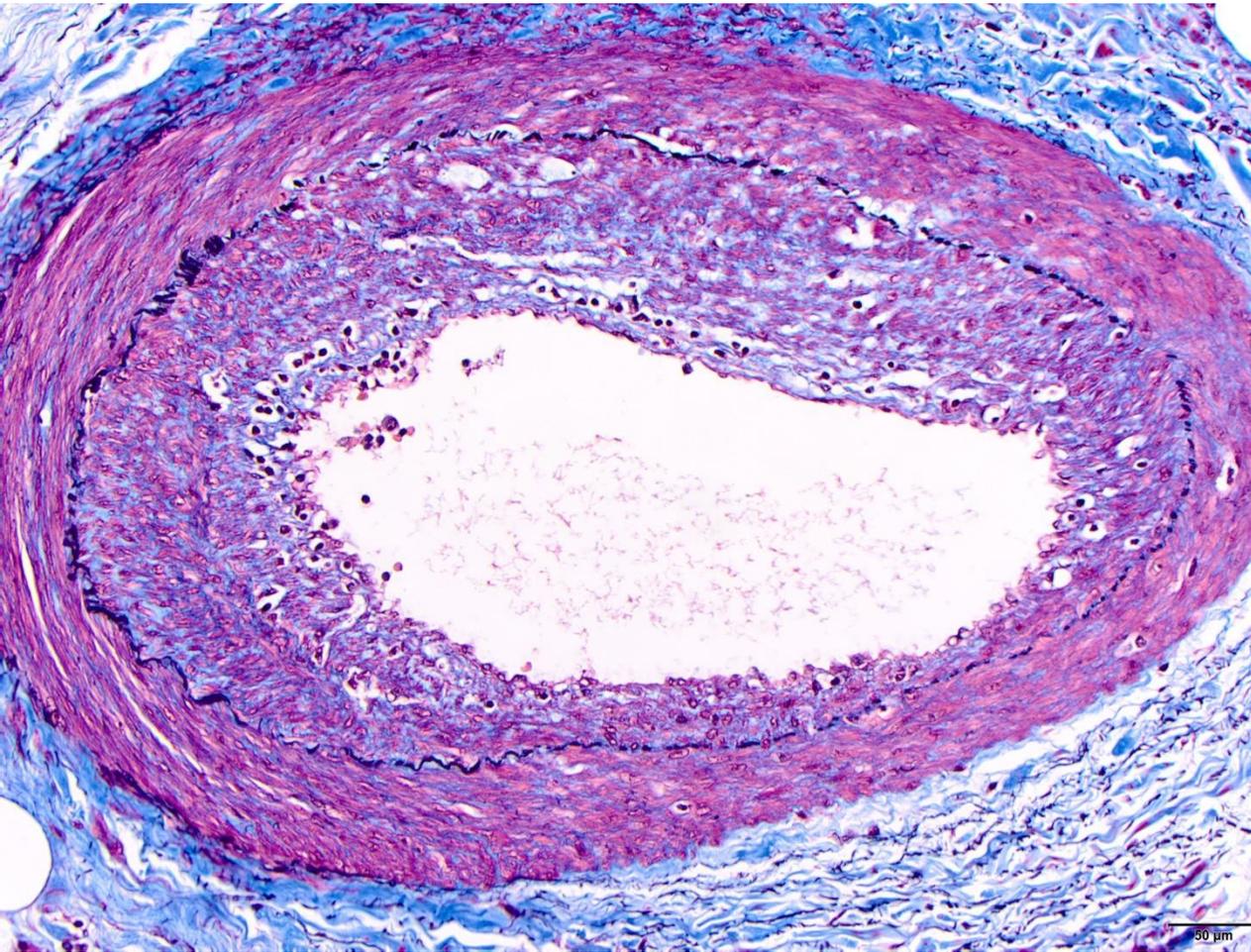


Trichrome/EVG

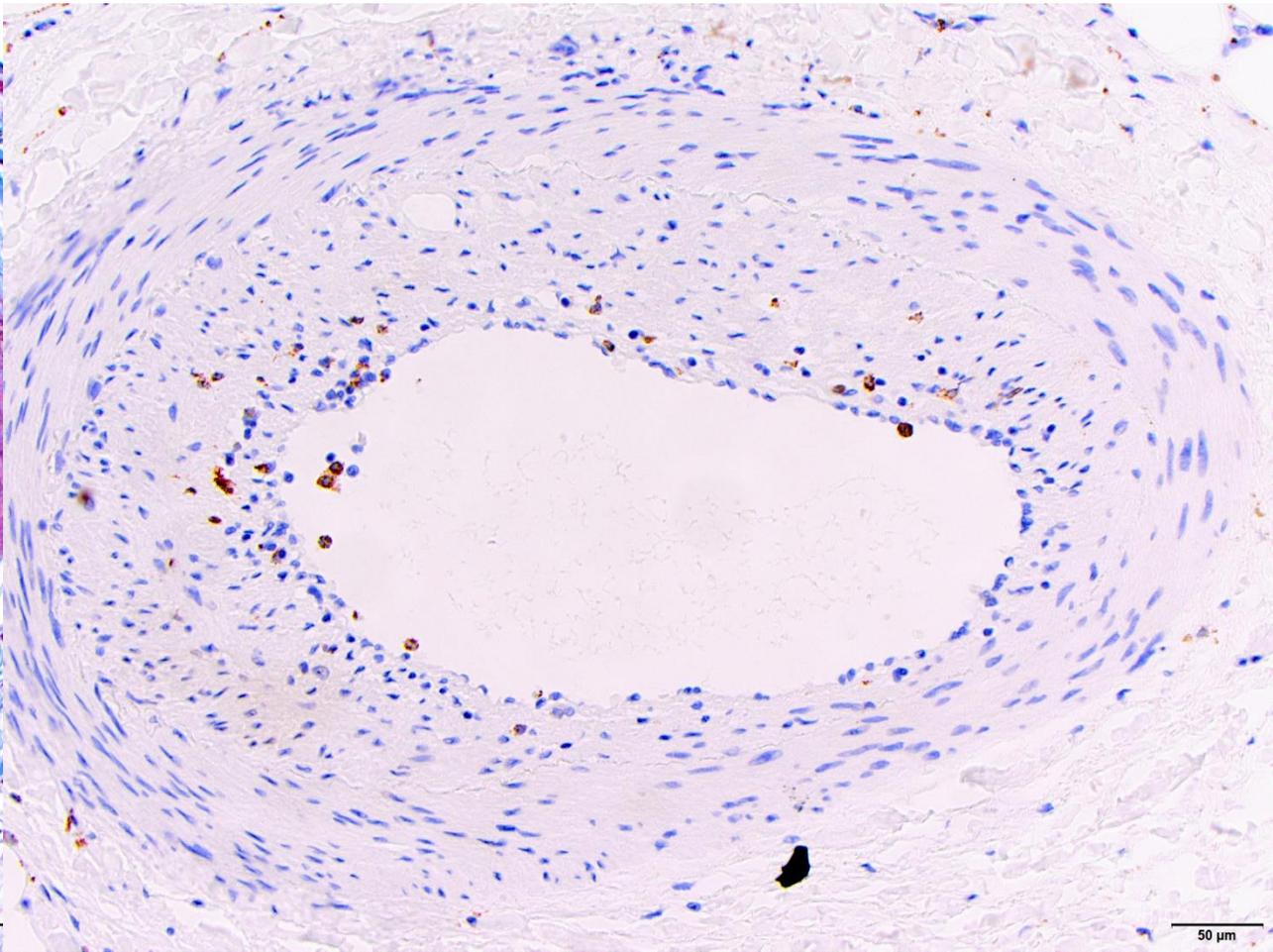


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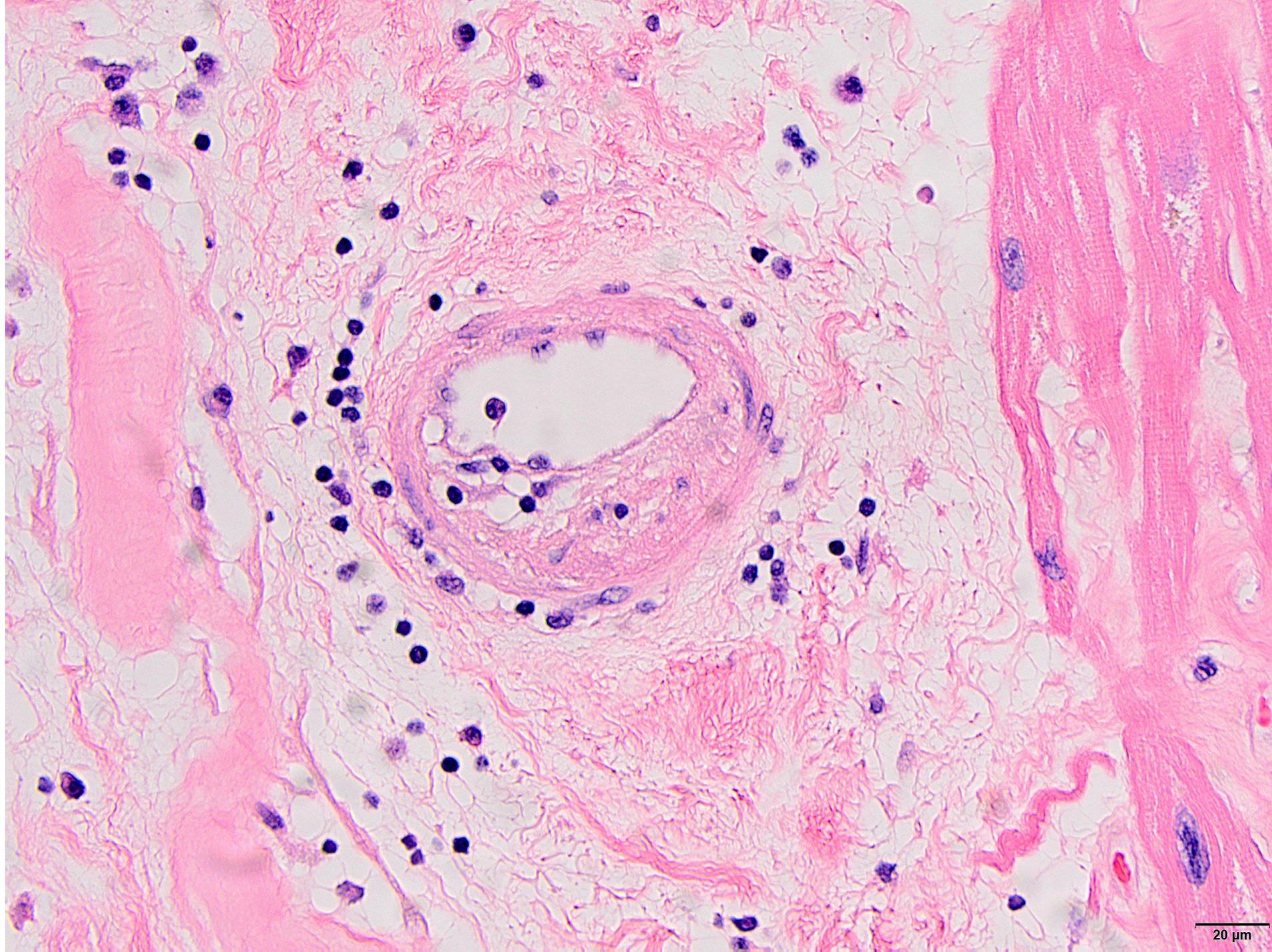


Trichrome/EVG



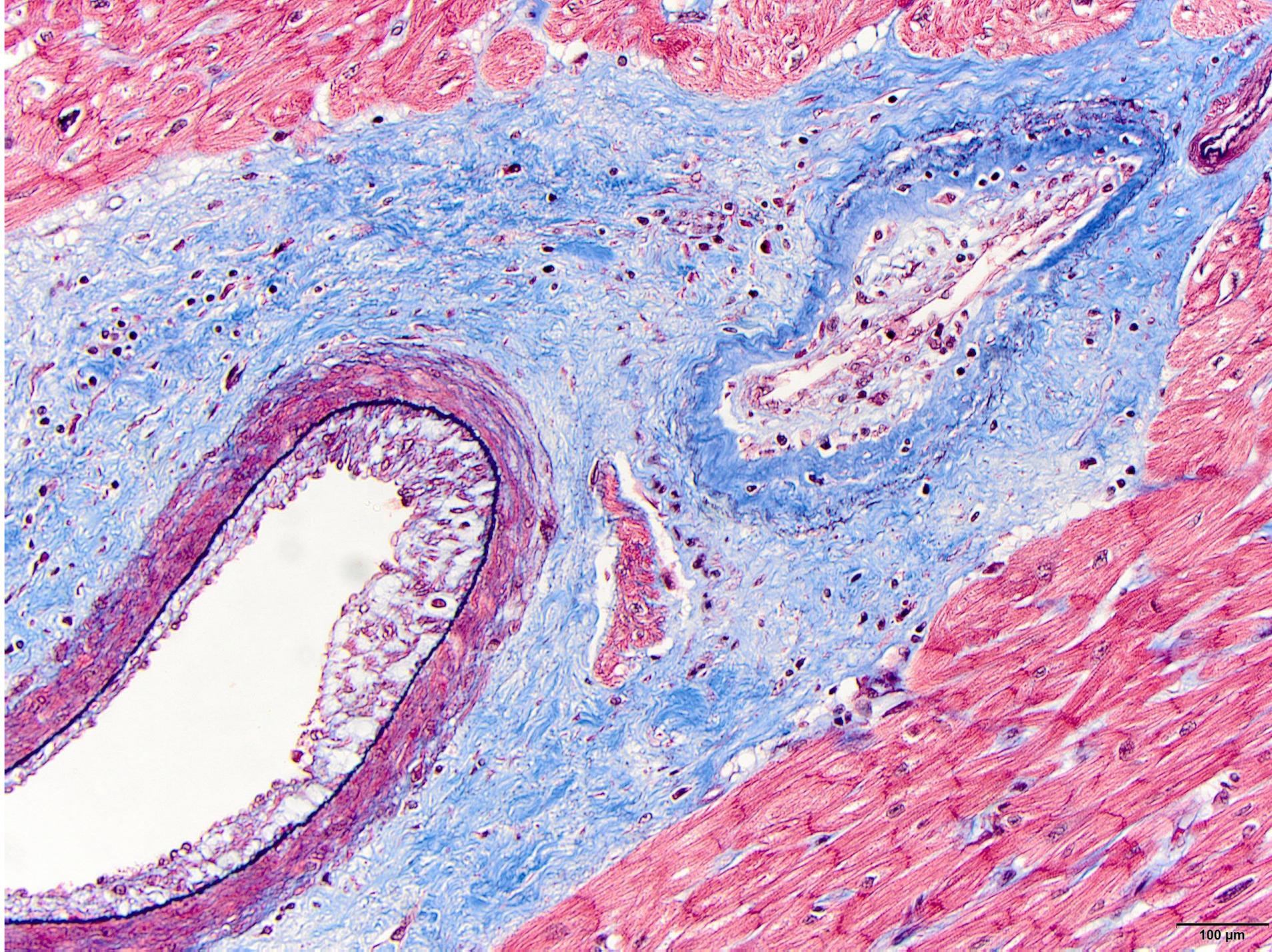
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Arteriolitis

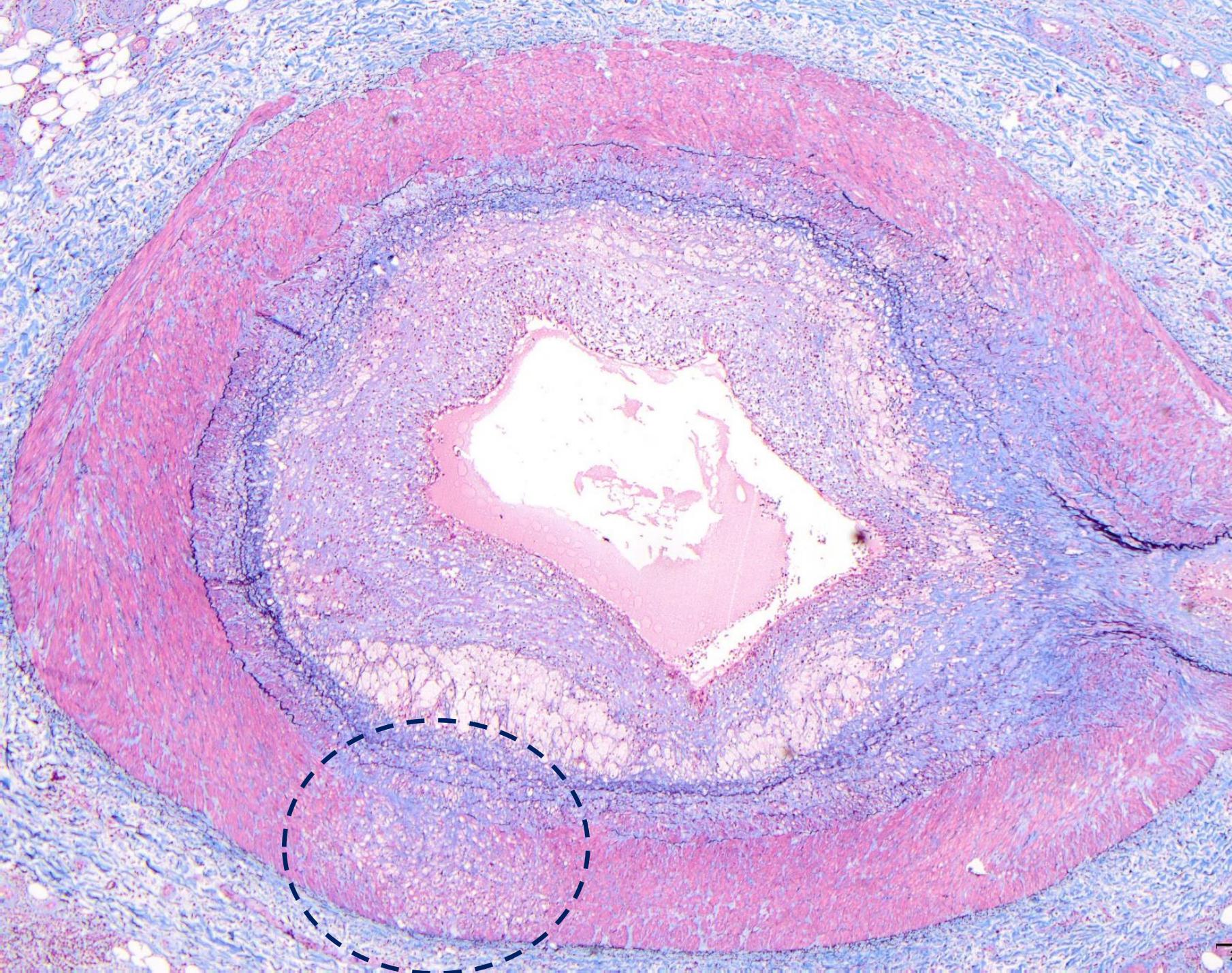
20 μ m



Phlebitis

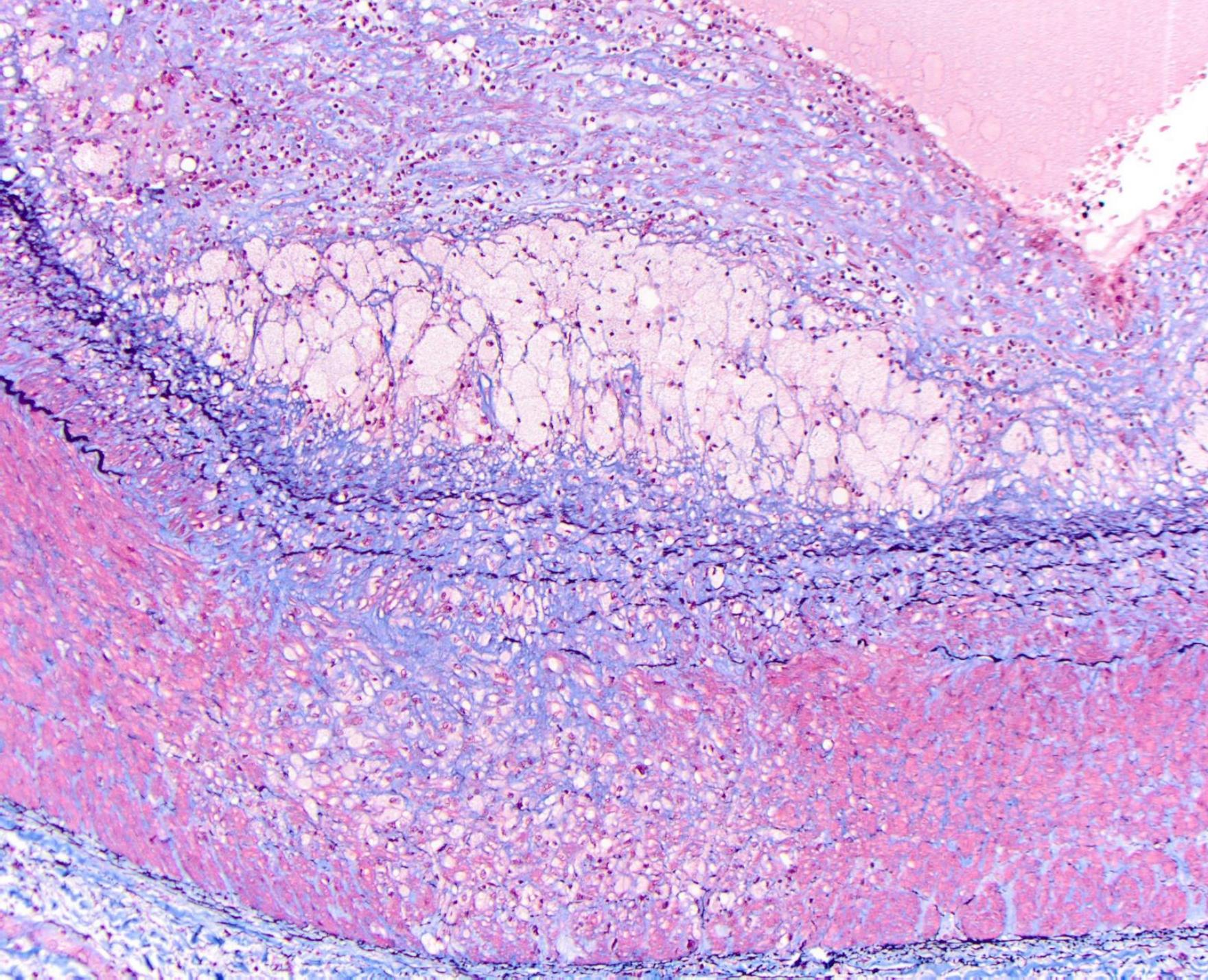
Trichrome/EVG

100 μm



Atherosclerosis

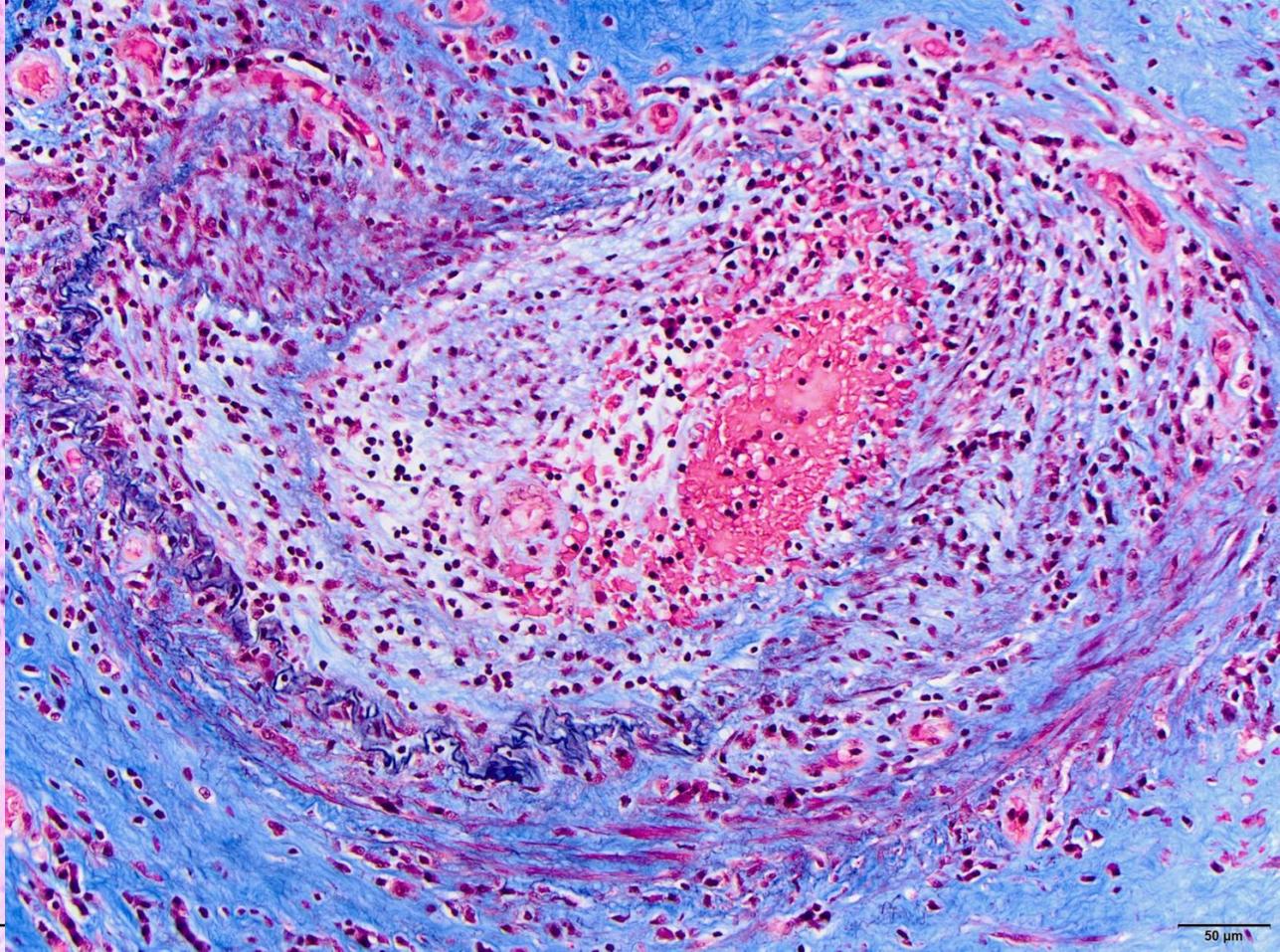
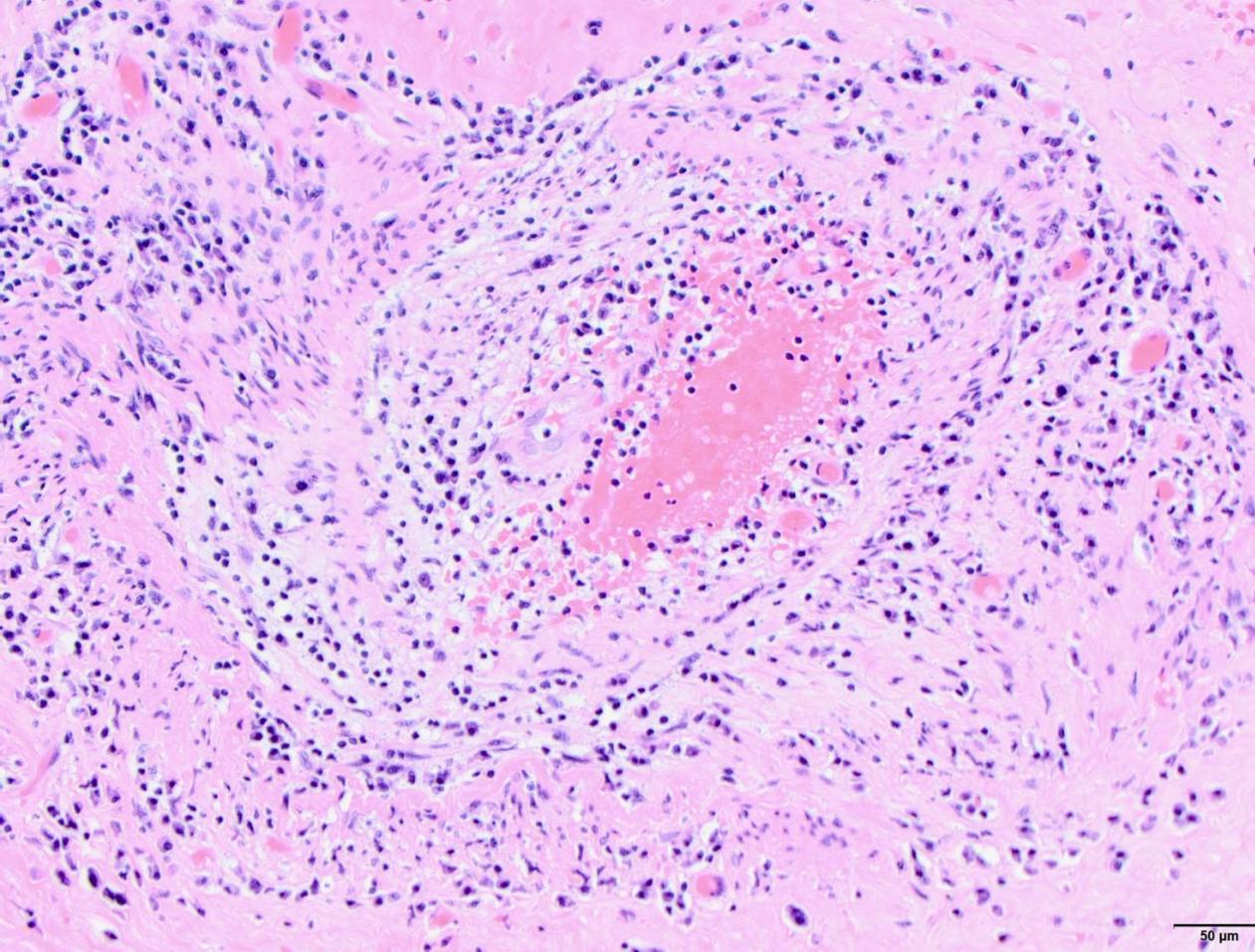
Trichrome/EVG



Medial inflammation
and fibrosis

Trichrome/EVG

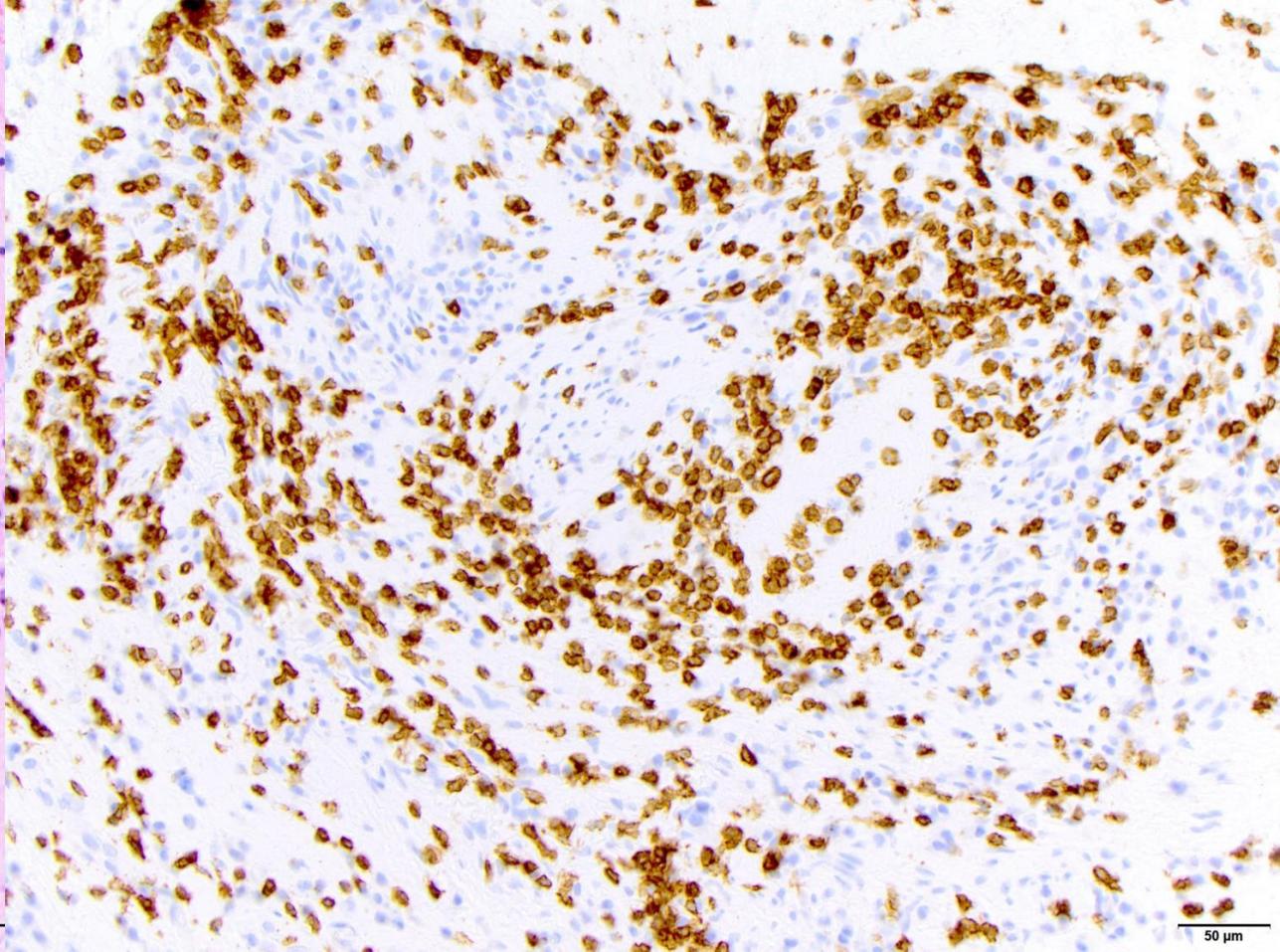
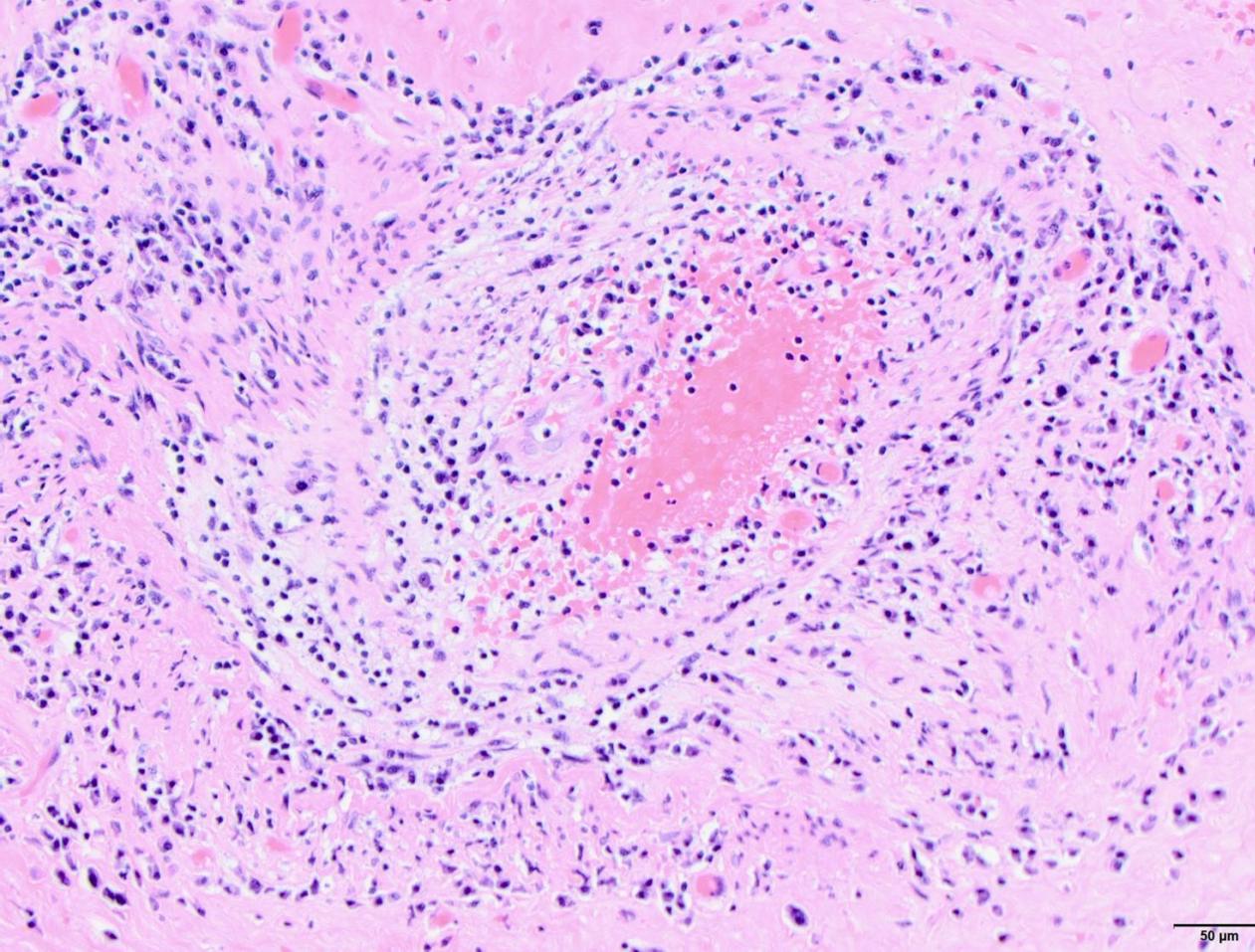
Full-thickness necrotizing vasculitis



Trichrome/EVG



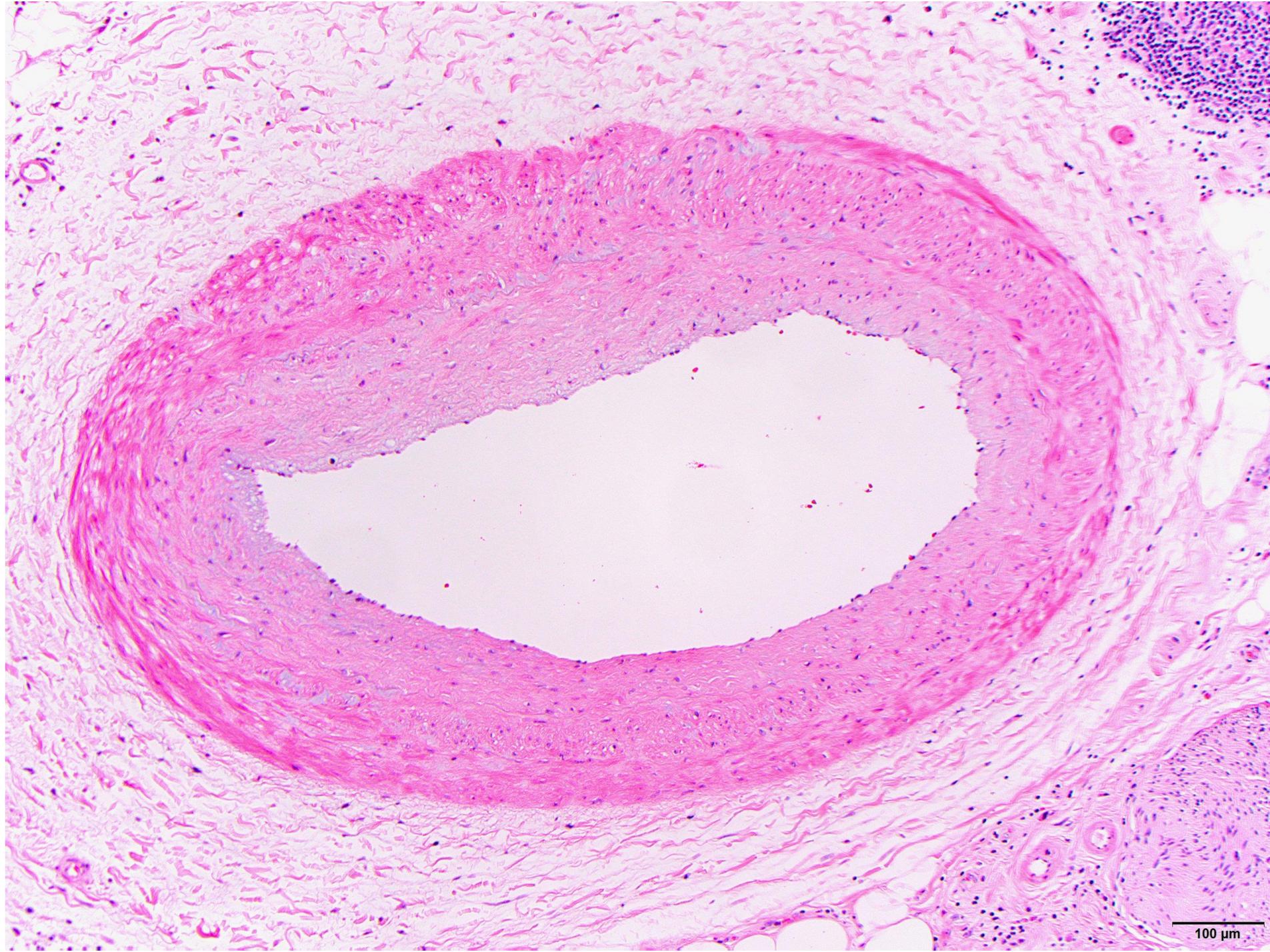
Full-thickness necrotizing vasculitis



The Three Pathologies of CAV

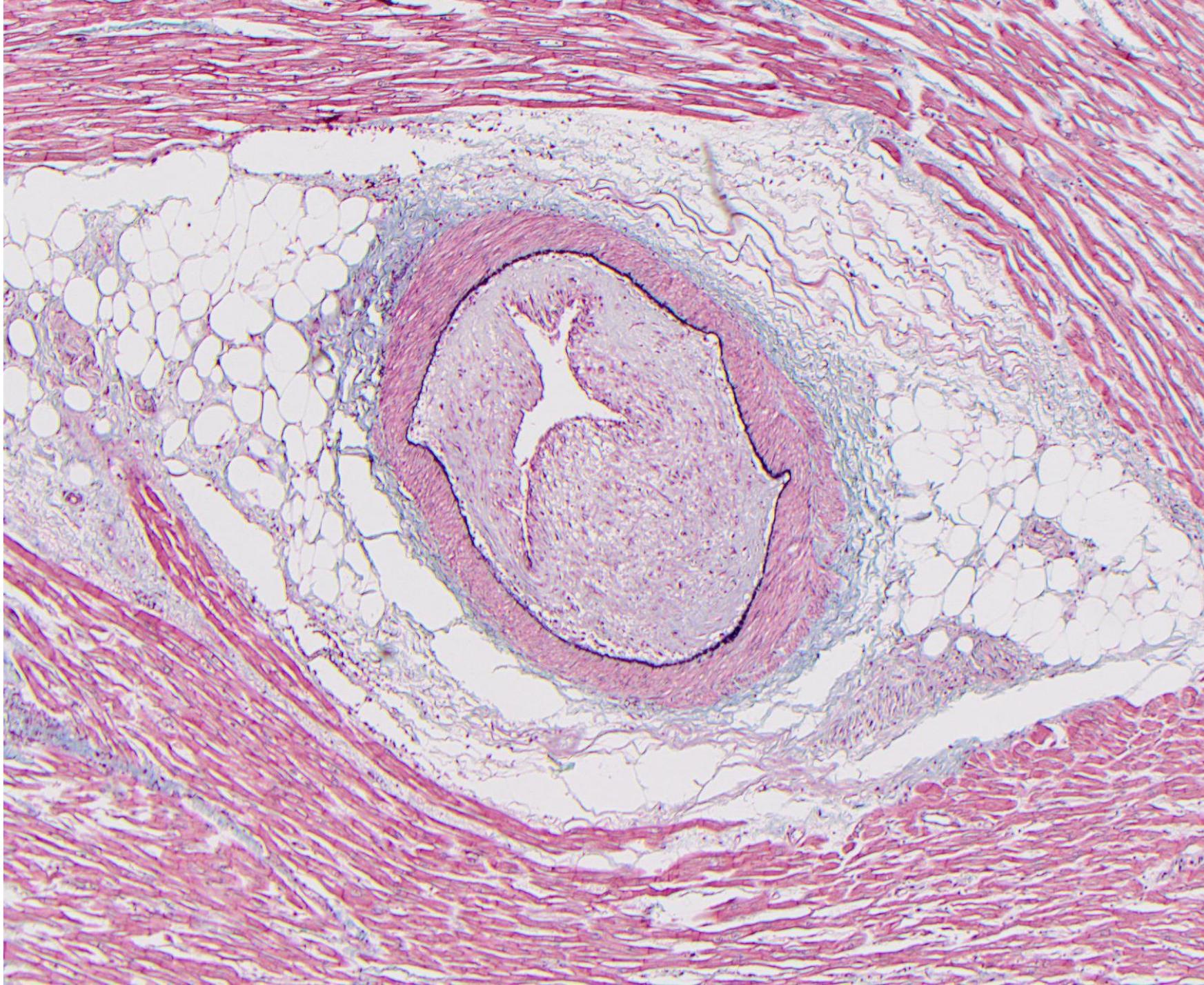
- Atherosclerosis
- Vascular inflammation
- Fibromuscular intimal hyperplasia





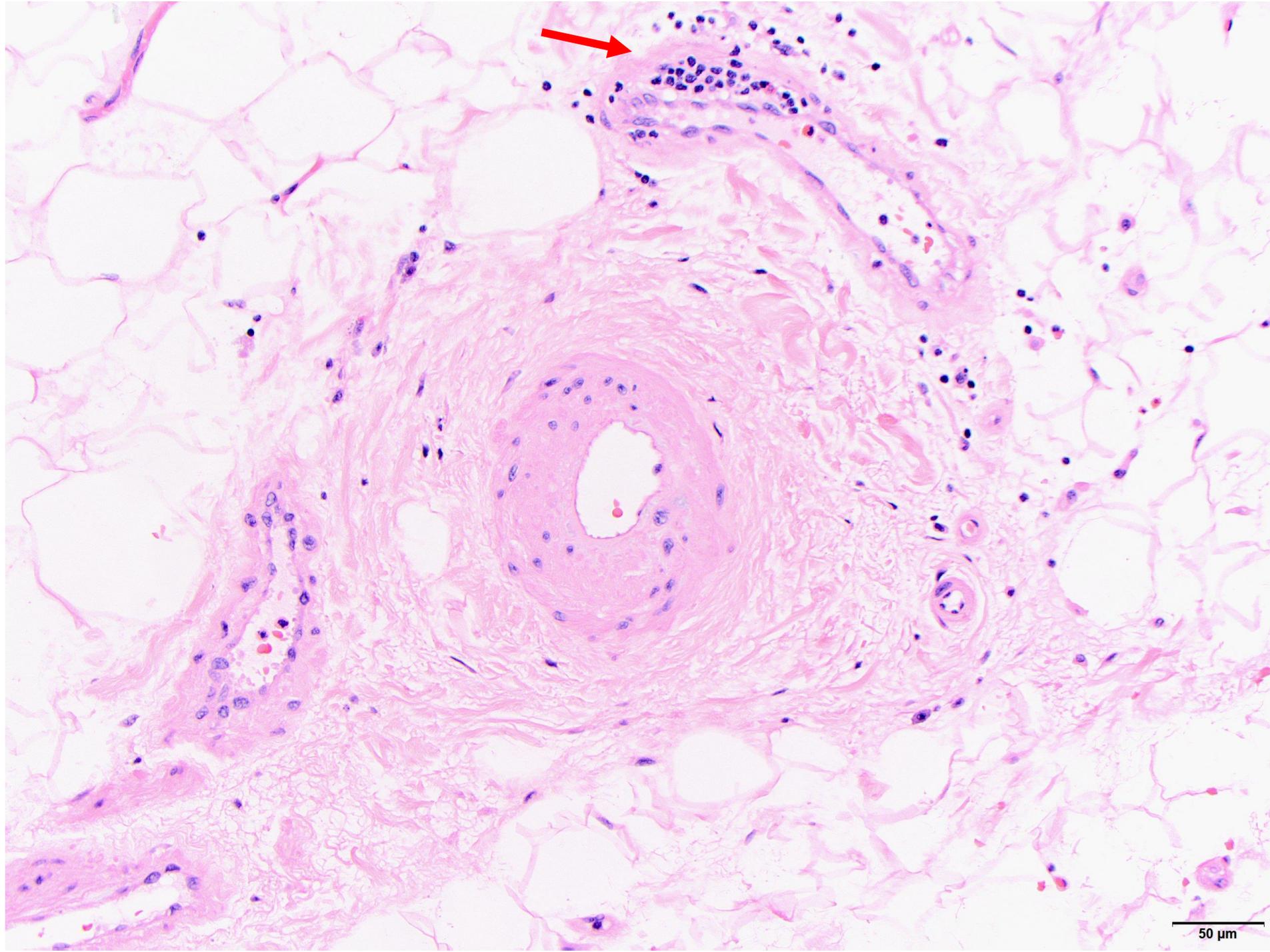
Fibromuscular proliferation without inflammation

100 μ m



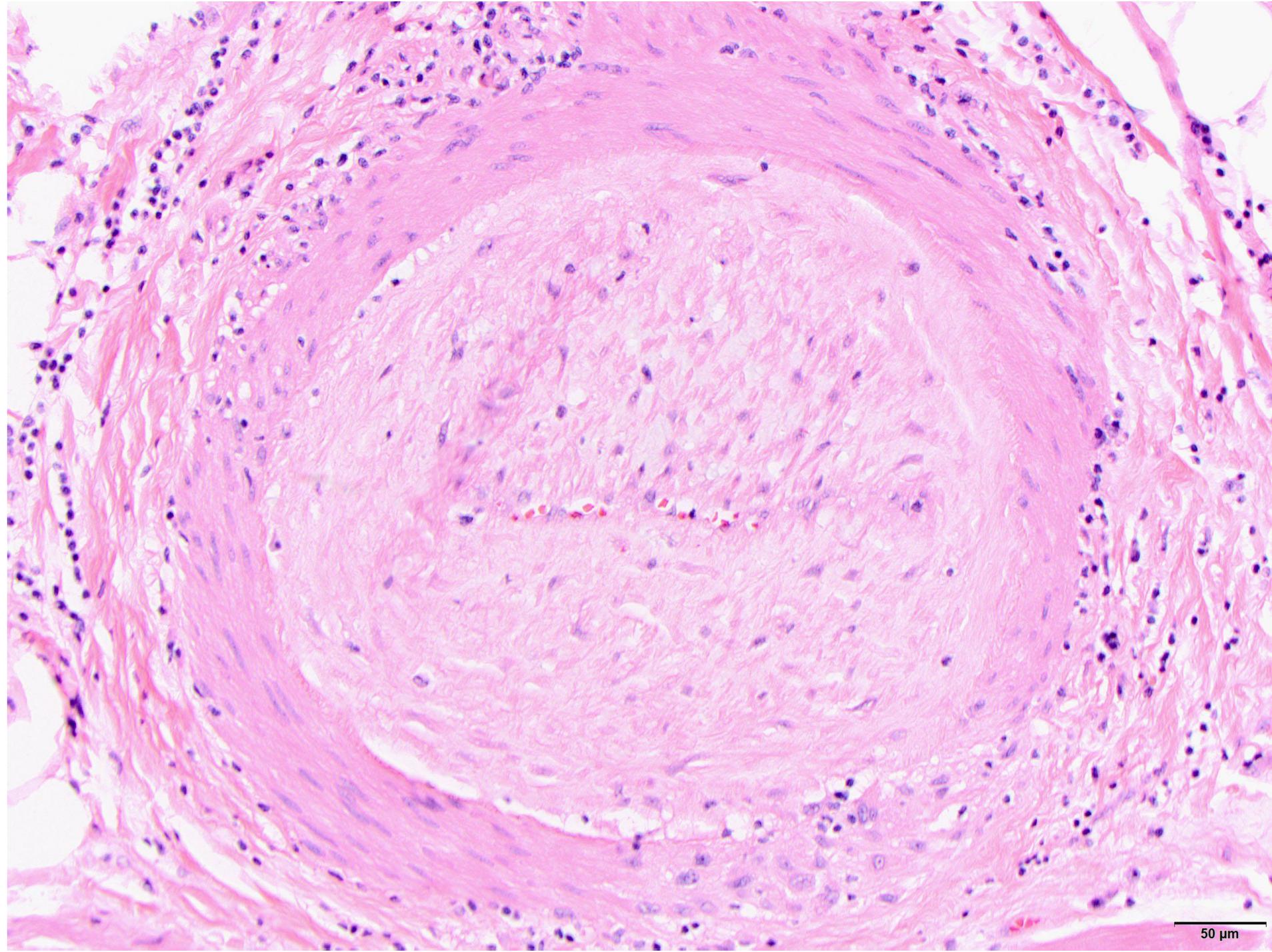
Intramyocardial artery

Trichrome/EVG



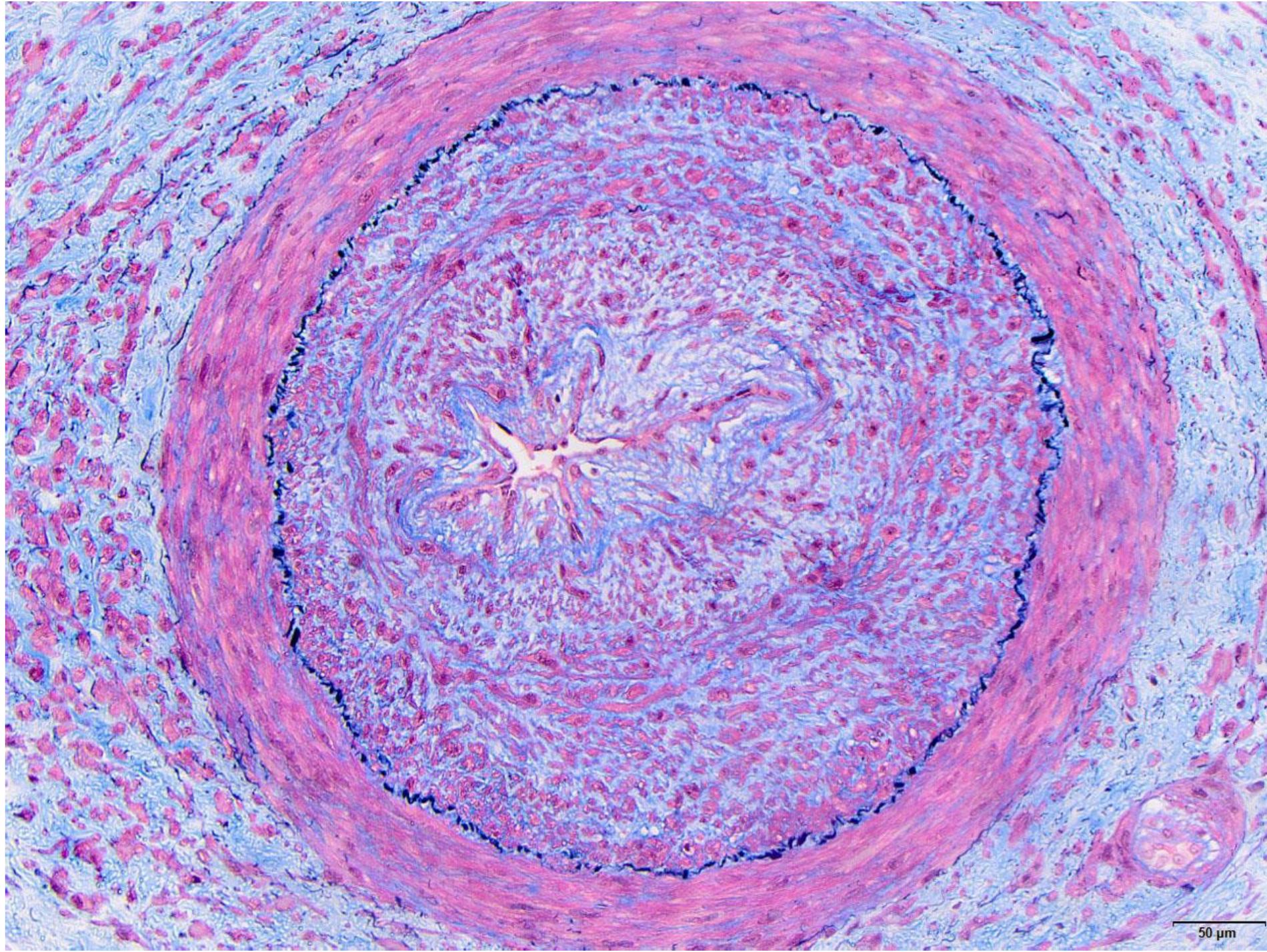
Arteriole

50 μ m



Occlusive
fibromuscular
proliferation

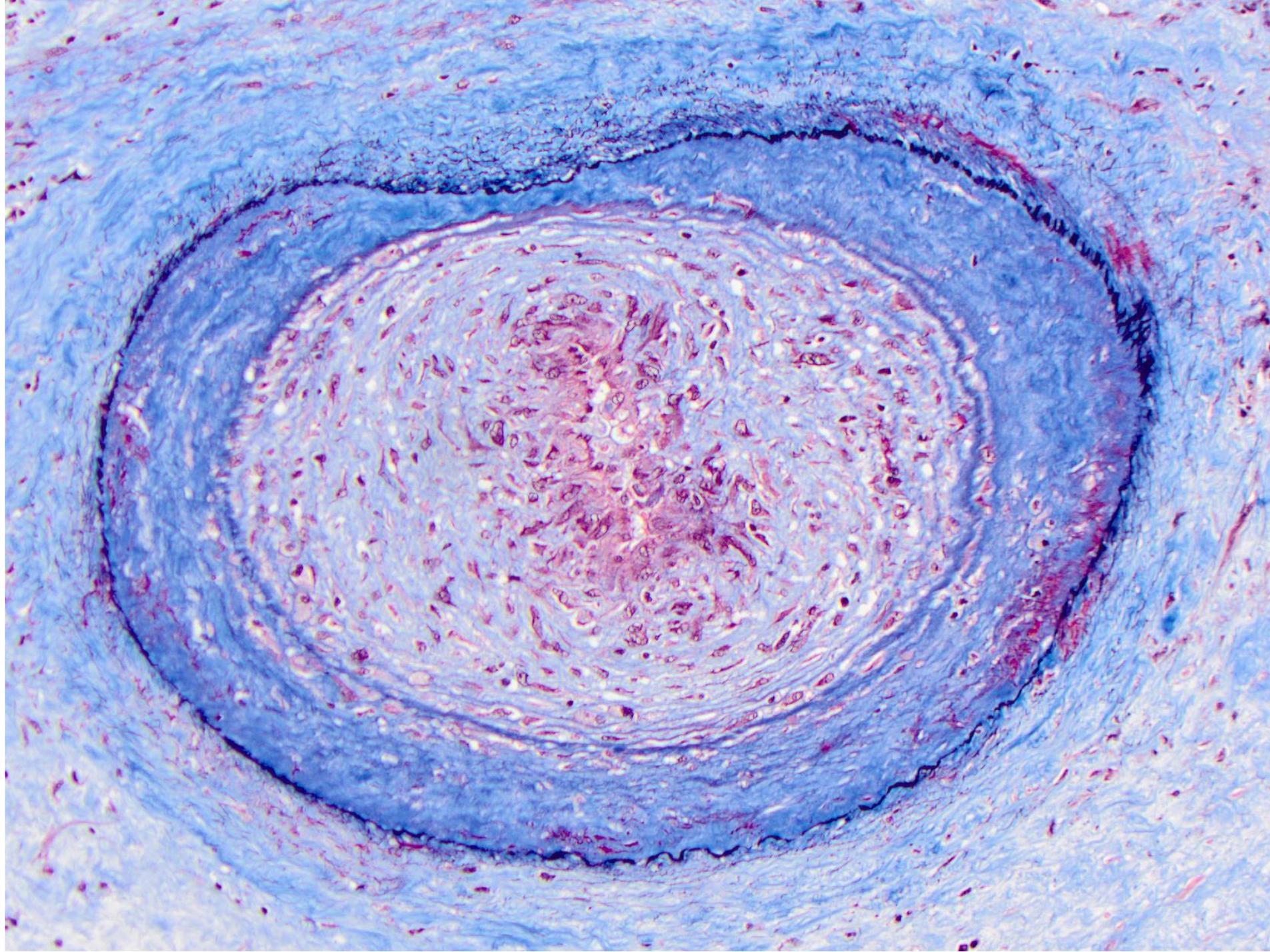
50 μ m



Occlusive
fibromuscular
proliferation

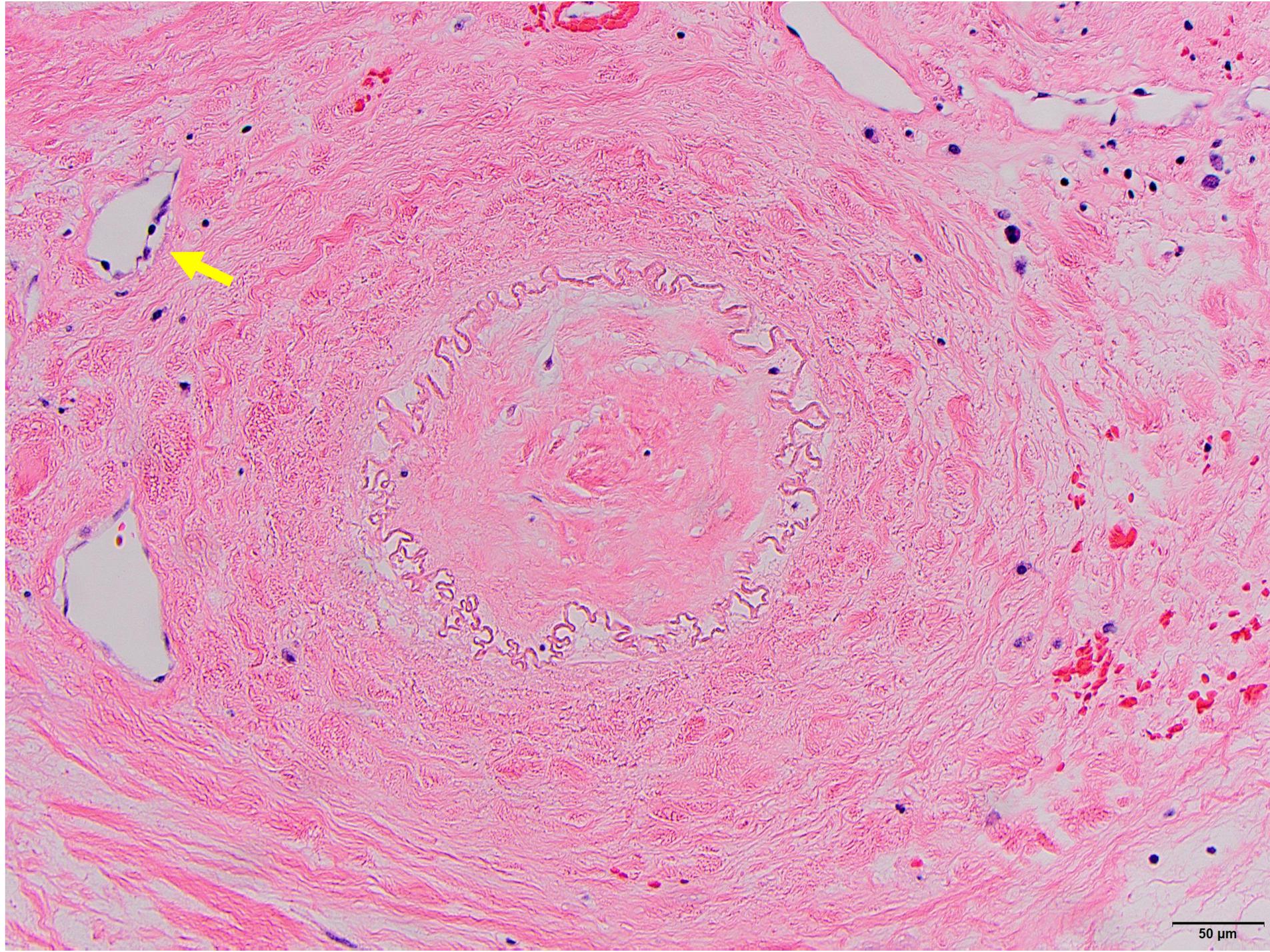
Trichrome/EVG

50 μ m



Mural fibrosis

Trichrome/EVG



Late lesion

50 μ m

The Heart with CAV

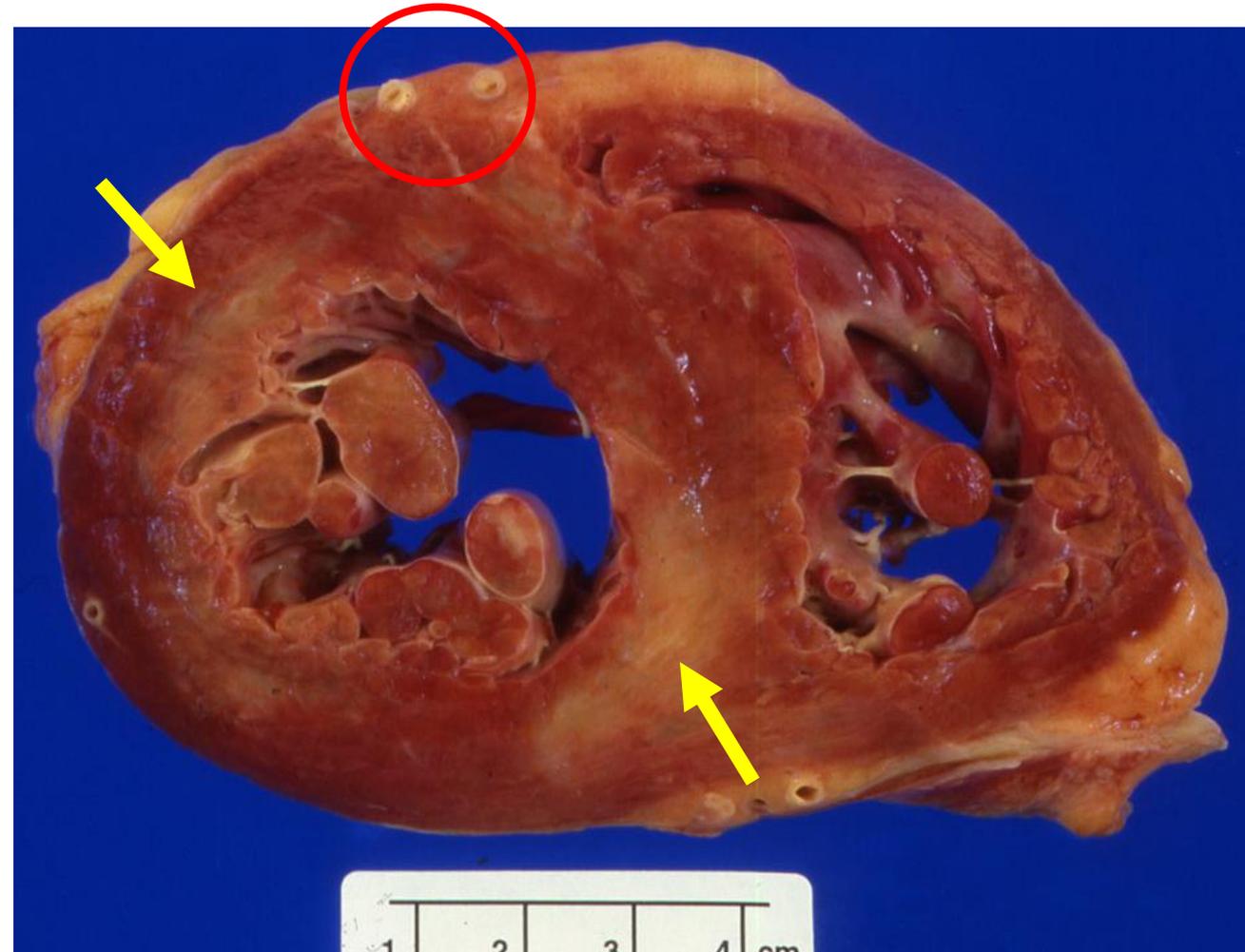


David Geffen
School of Medicine

UCLA Health

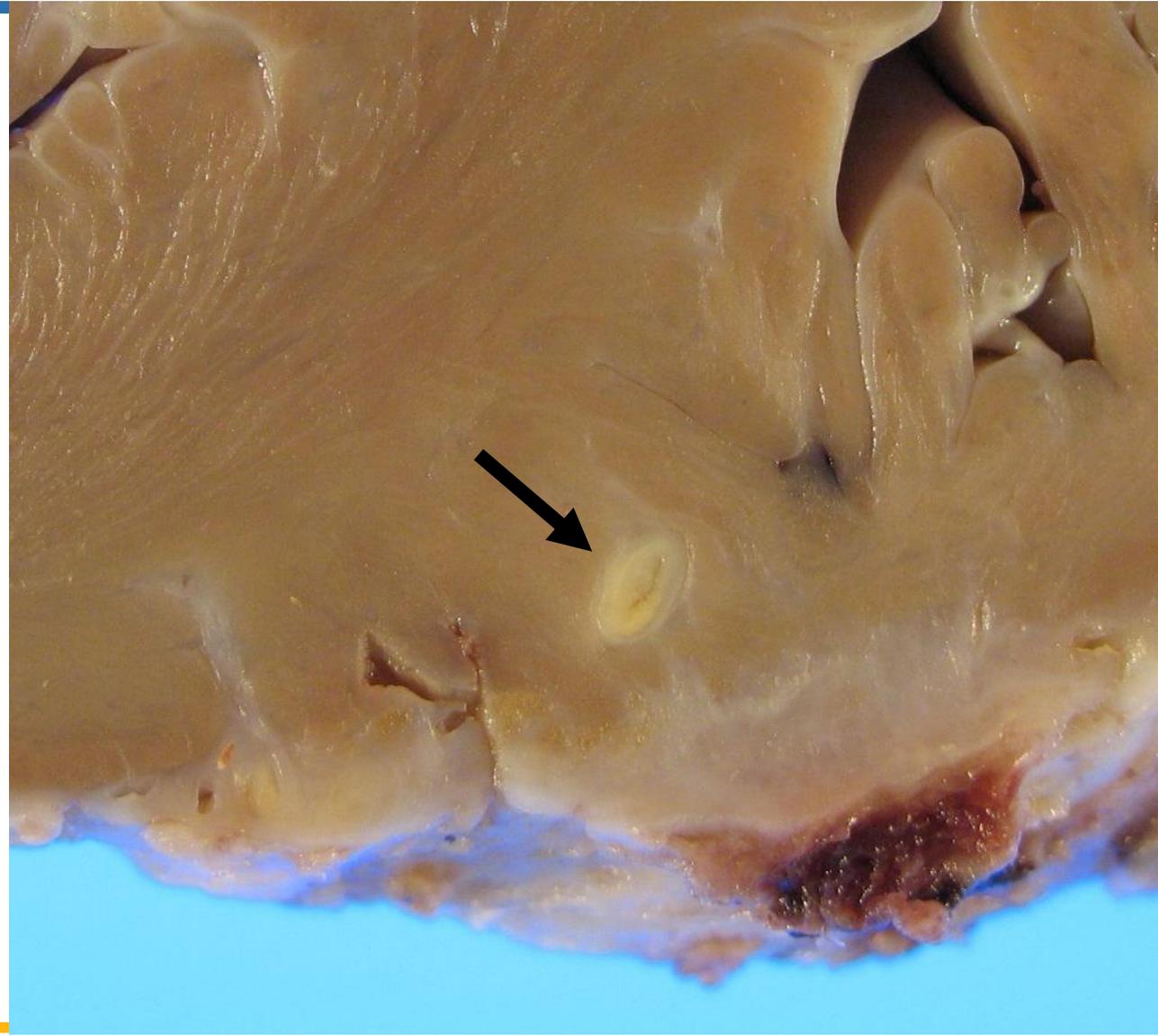
Gross Findings

- Myocardial infarction in a coronary distribution
- Epicardial coronary atherosclerosis



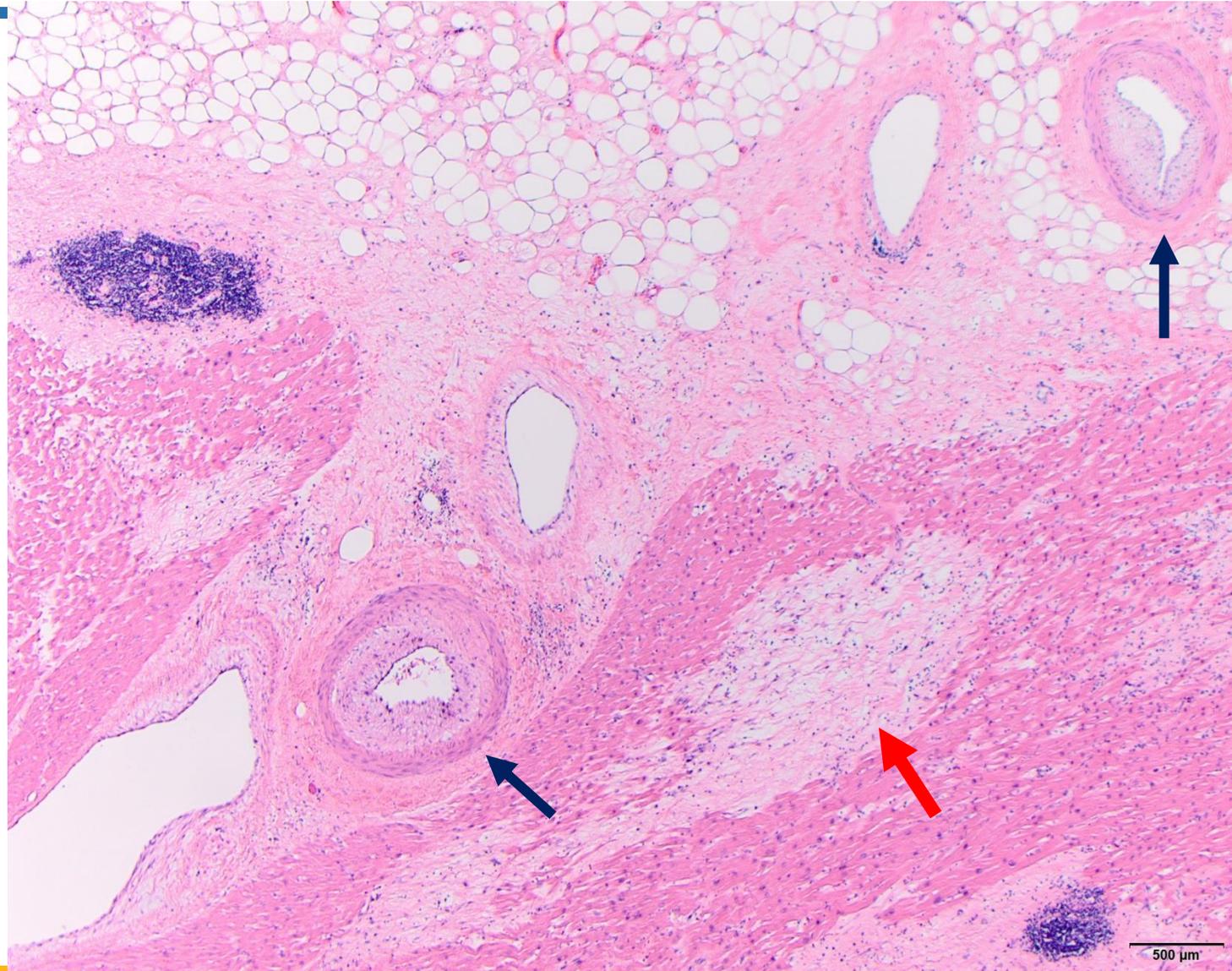
Gross Findings

- Myocardial infarction in a coronary distribution
- Epicardial coronary atherosclerosis
- Fibromuscular intimal thickening of intramyocardial arteries

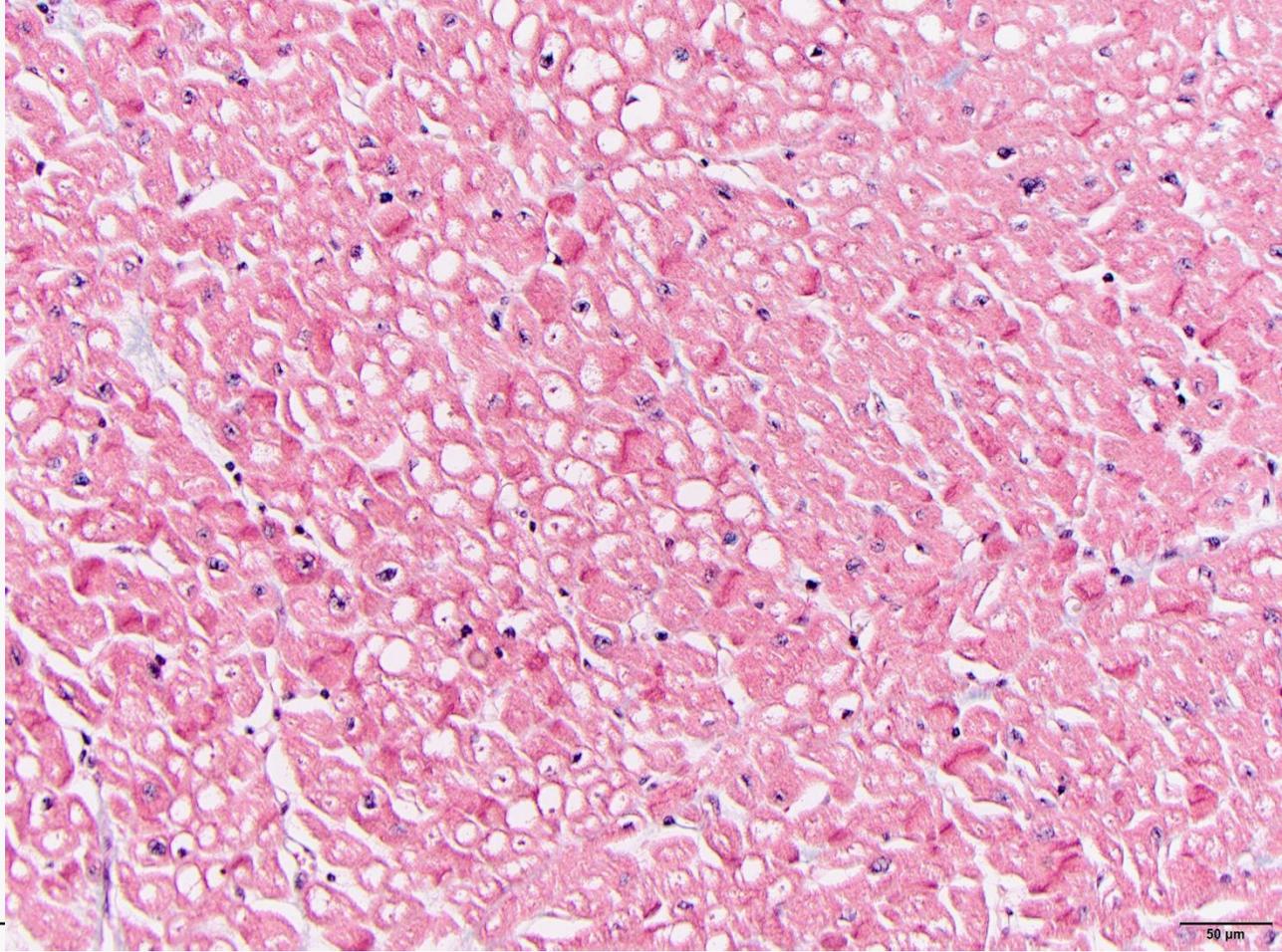
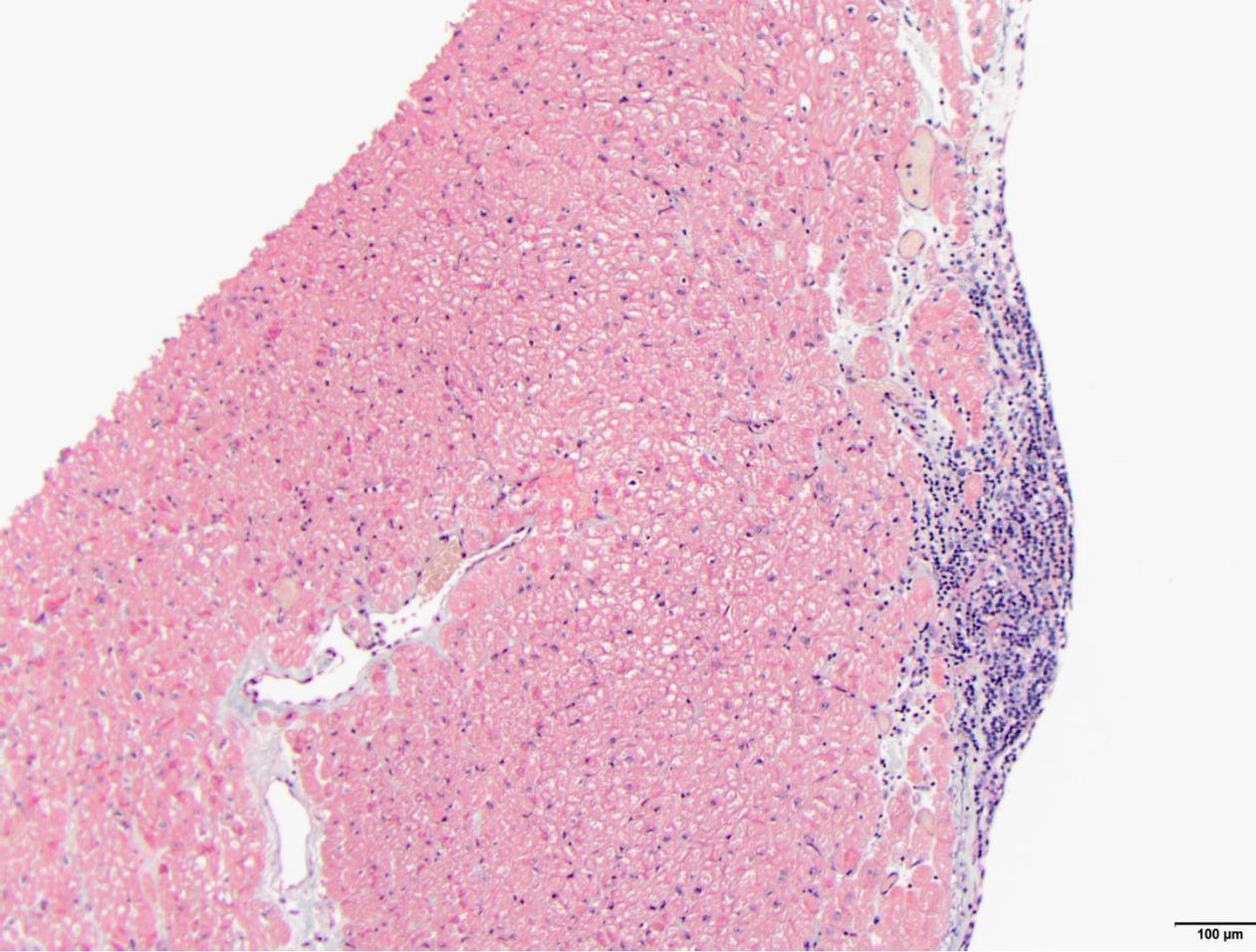


Microscopic Findings

- Vasculopathy
- Replacement fibrosis

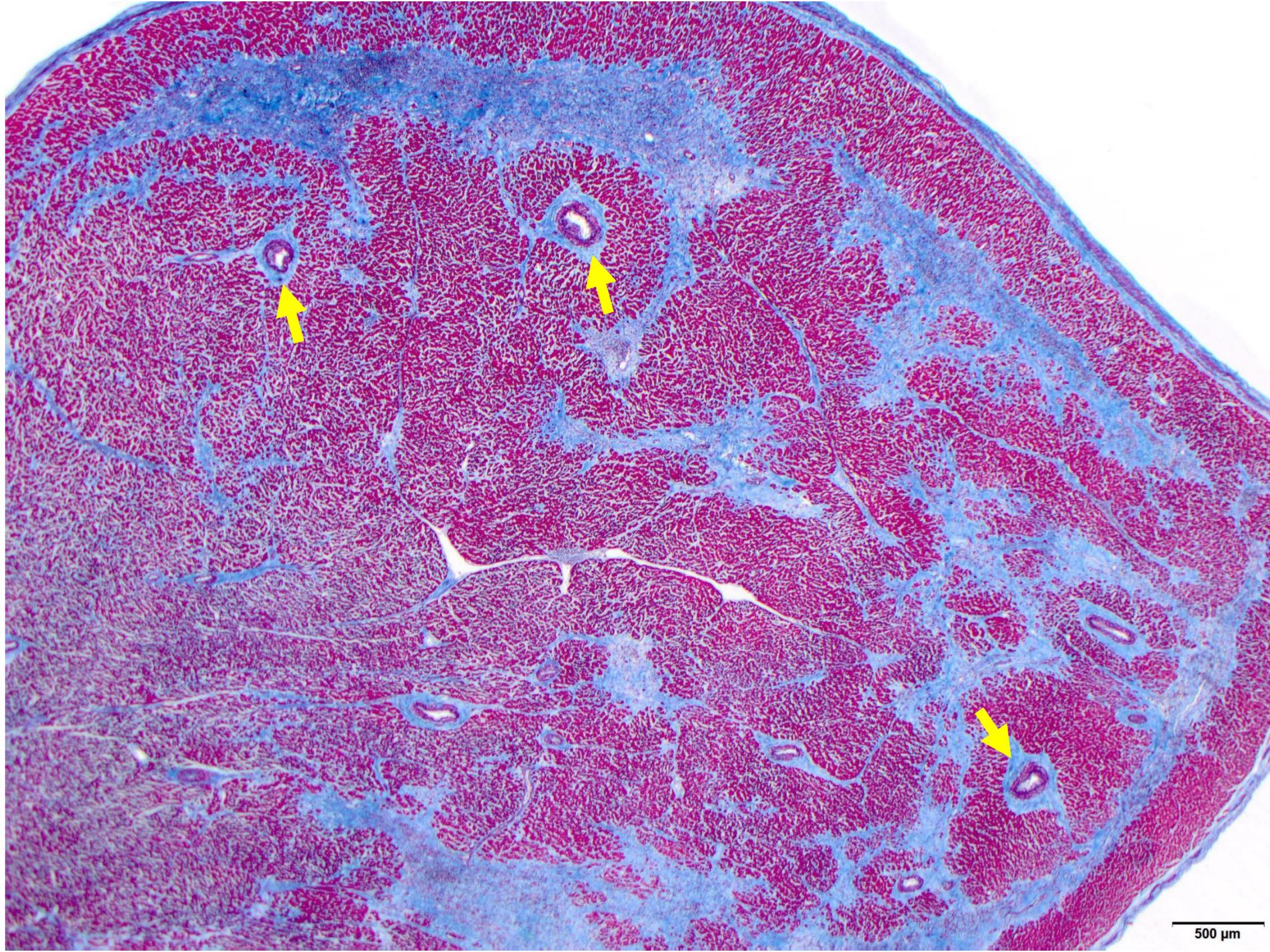


Subendocardial vacuolar degeneration



Trichrome



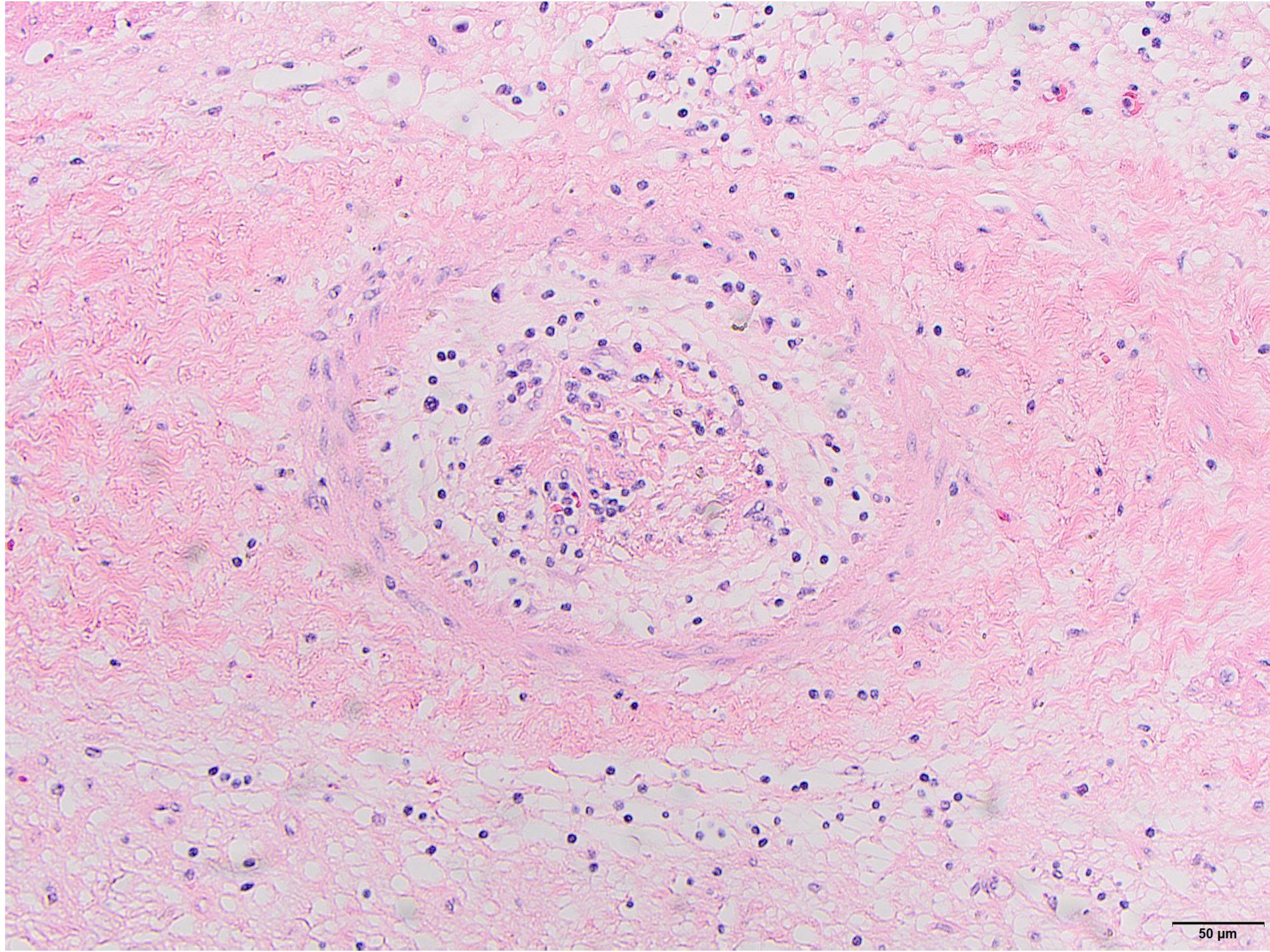


Subendocardial
fibrosis

Vasculopathy

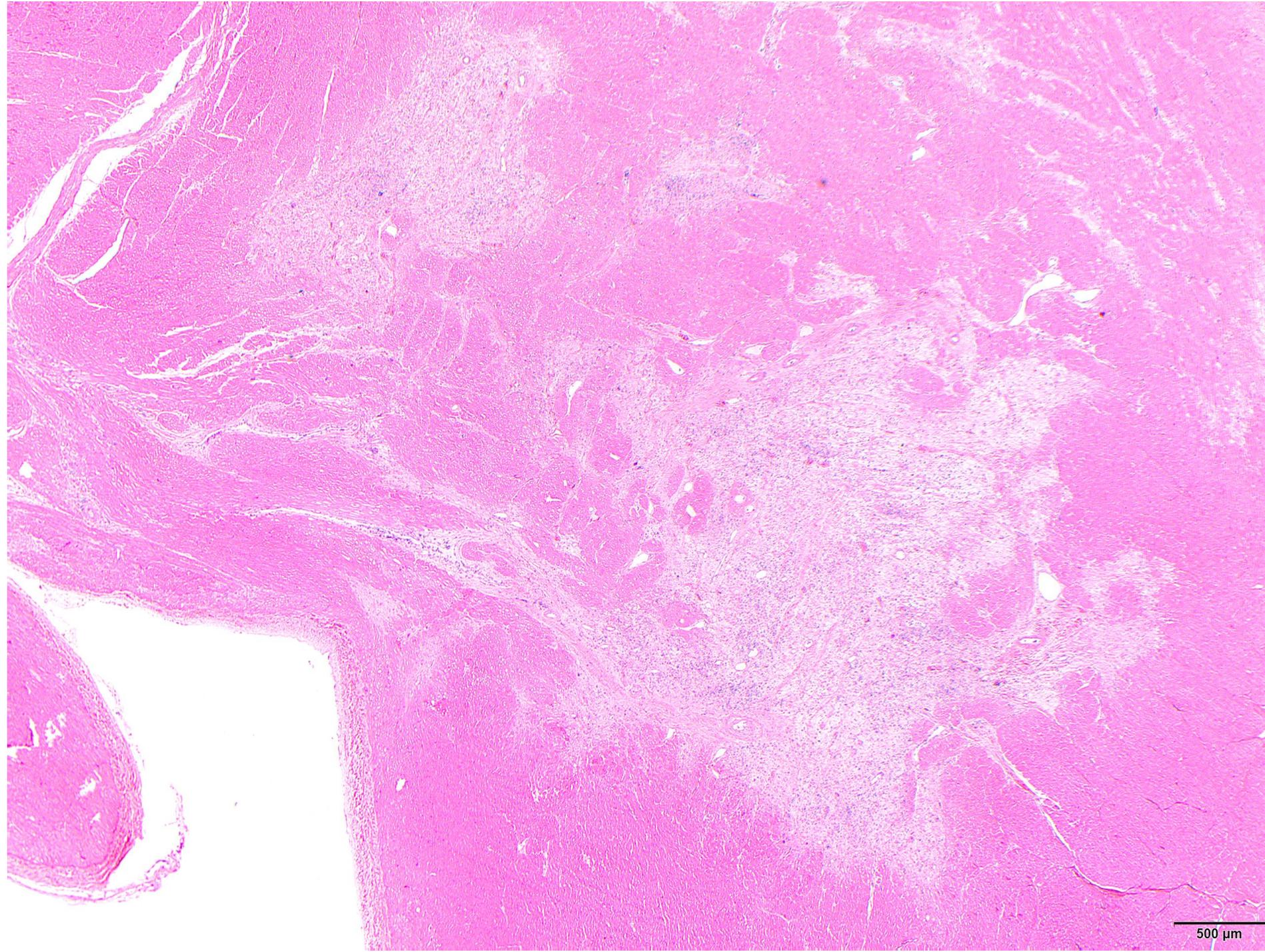
Trichrome/EVG

500 μ m



Organizing
thrombus

50 μ m



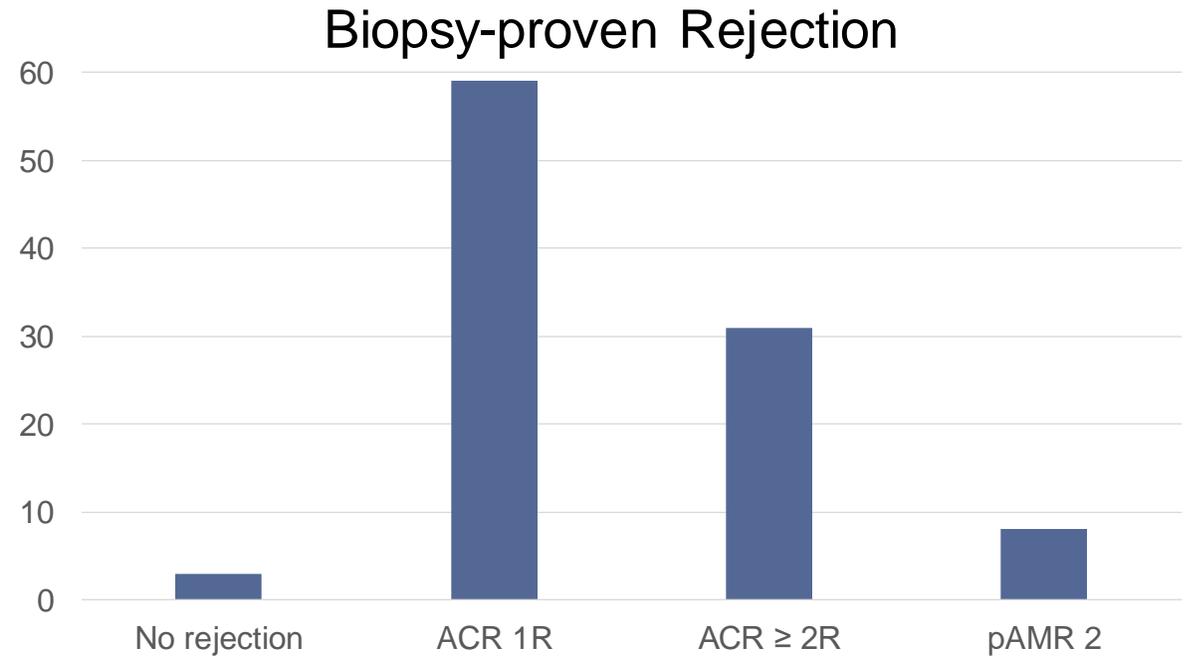
Healing myocardial infarction

Observations

- We examined 64 explanted adult and pediatric donor hearts with severe CAV

	Adult males (45)	Adult females (9)	Pediatric (10)
Time to re-transplant (months)	90	74	67
Number of Biopsies	25	26	16
Episodes of ACR	9	8	3

Numbers reflect the mean



Observations

- Atherosclerosis was ubiquitous
- Intramyocardial involvement was surprisingly focal
- Inflammation was more severe and more common in the tunica intima
- Degree of intimal inflammation was inversely related to the time-to-re-transplantation



CAV: Summary

- Cardiac allograft vasculopathy is a multifaceted disease composed of 3 major pathologies



CAV: Summary

1. Atherosclerosis

- Adult and pediatric populations

2. Vascular inflammation

- Endothelitis to full-thickness necrotizing vasculitis

3. Fibromuscular intimal hyperplasia

- Epicardial and intramyocardial vessels
- Arteries, veins, venules, and arterioles



Thank you!



David Geffen
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