NYU Grossman Long Island School of Medicine

DEPARTMENT OF PATHOLOGY

Short Report in Pathology

Organ system: Heart

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10/29/2023

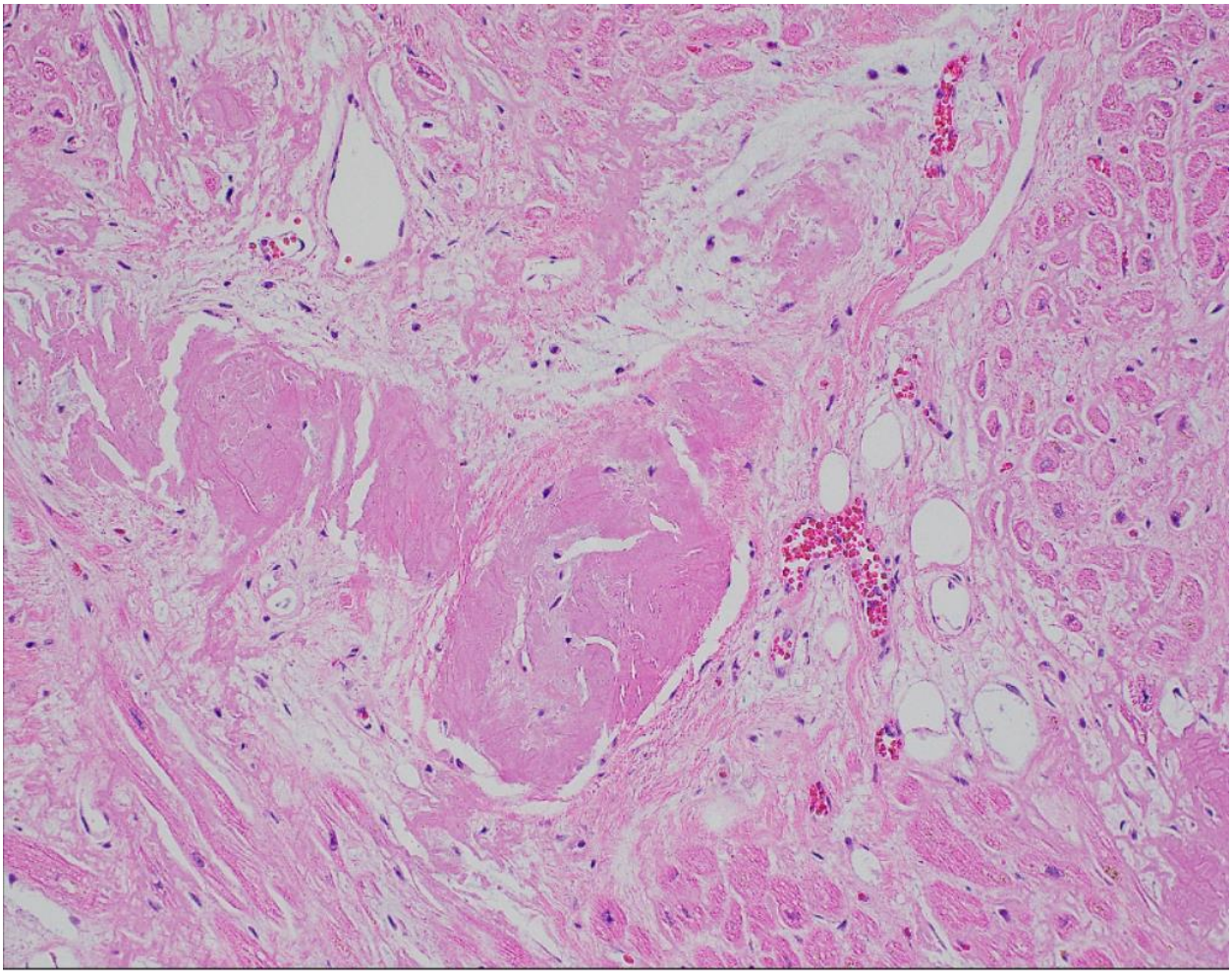
History:

The decedent is a 60+ year old male with past medical history of atrial fibrillation, biventricular heart failure, hypertension, hyperlipidemia (HTN), who was admitted to an outside hospital for congestive heart failure. His hospital course was complicated by renal failure. Later on, the patient developed shock, suffered a cardiac arrest, and was found unresponsive and pulseless. An autopsy was performed. The heart was enlarged (heart weight 835 g) with diffuse thickening.

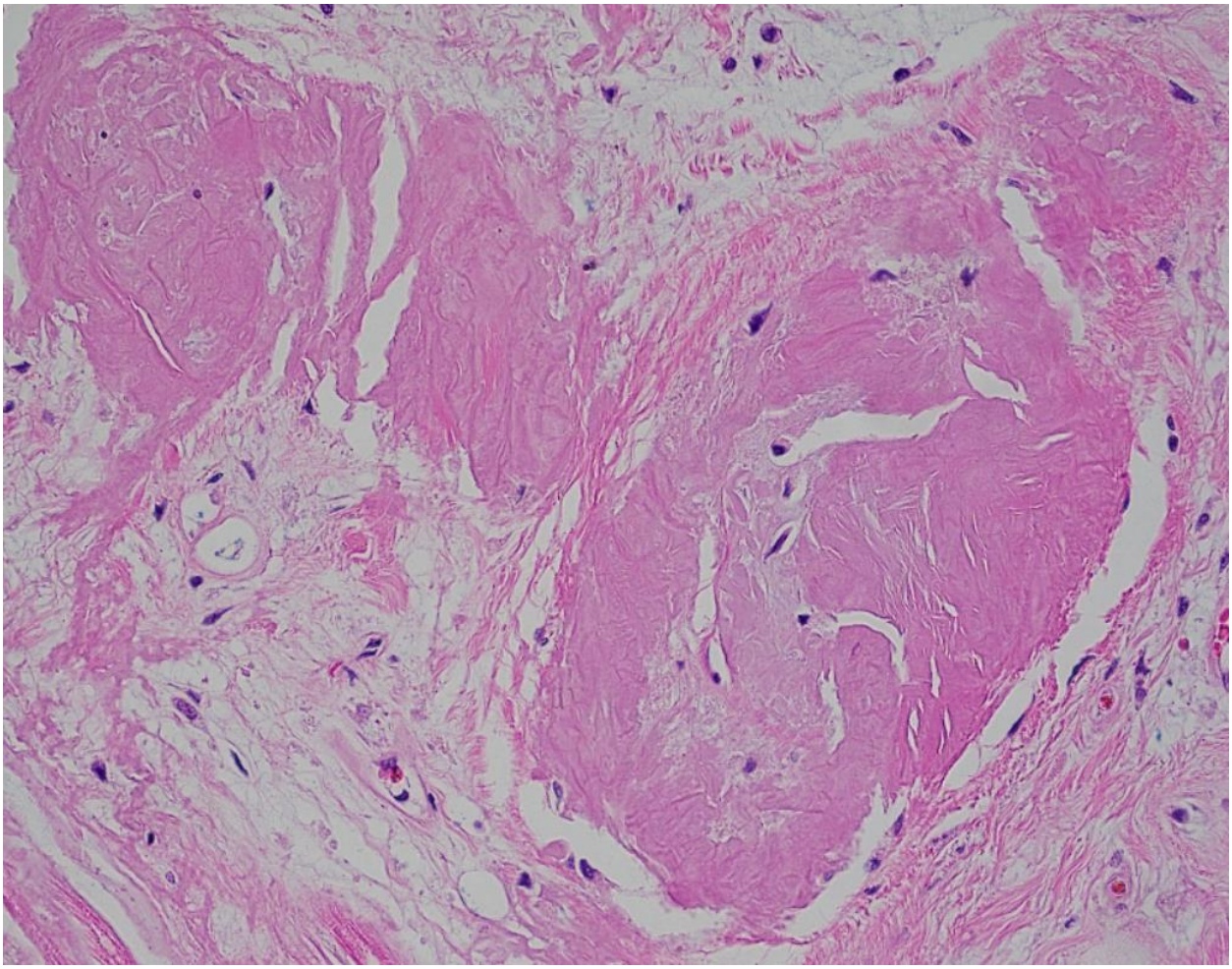
Gross Description of the Heart:

The right ventricle measures 0.5 cm in thickness; the left ventricle measures 1.2 cm in thickness. The interventricular septum measures 1.0 cm in thickness. Significant aortic atherosclerosis is noted. The coronary arteries have moderate atherosclerosis.

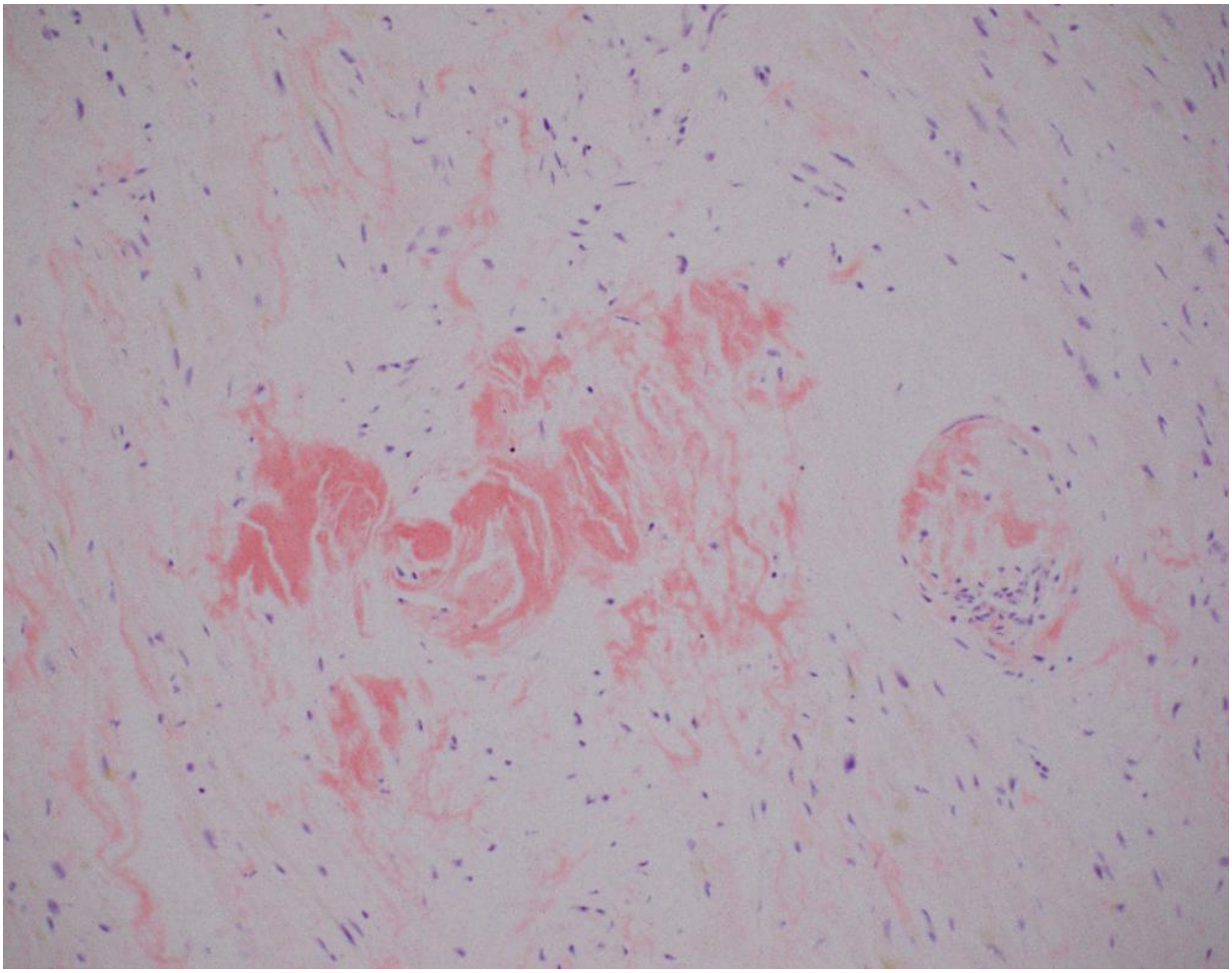
Microscopic Images:



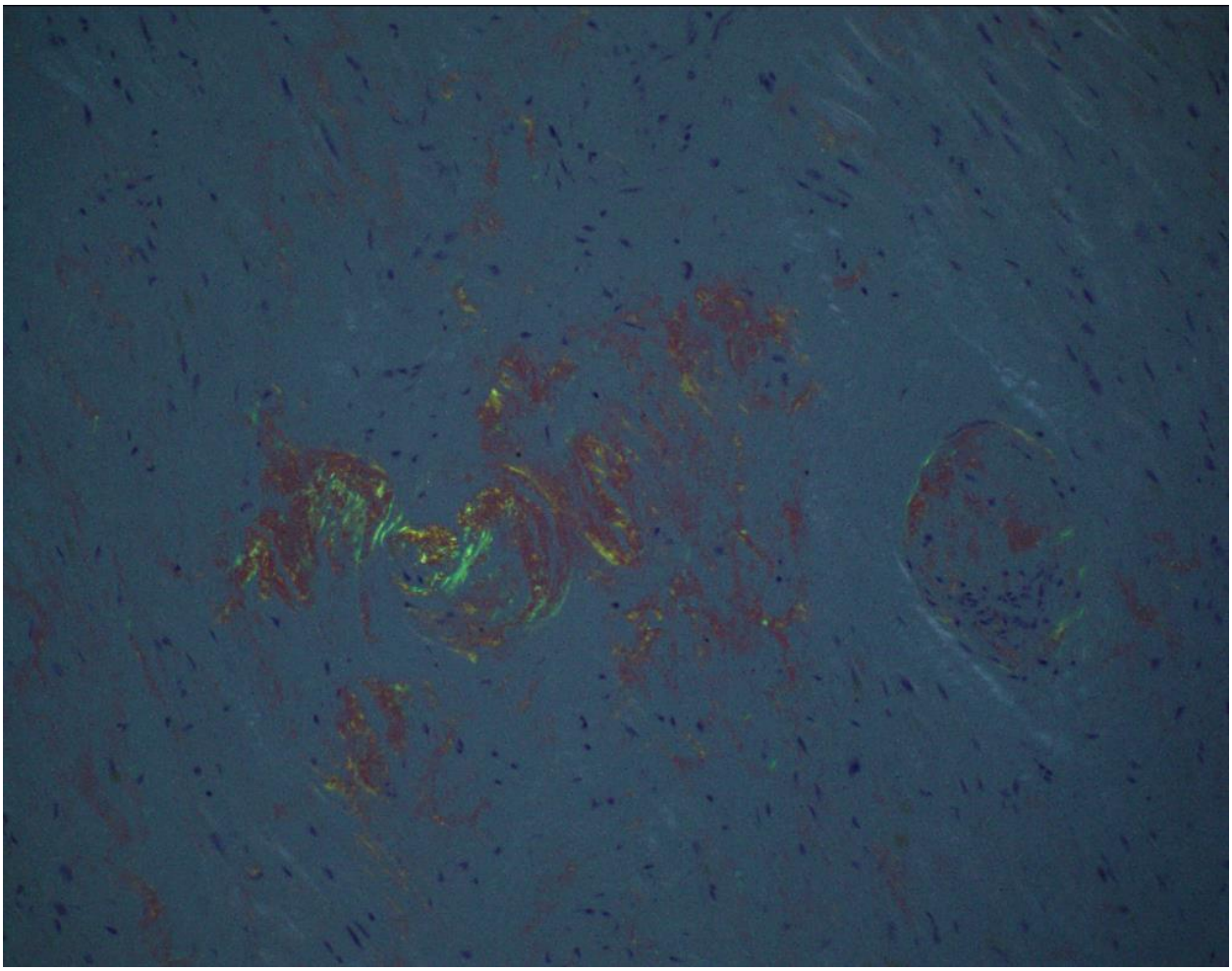
Amyloid deposition in cardiac tissue, showing interstitial accumulation of extracellular light eosinophilic, pale-pink, acellular, amorphous and smudgy material. The adjacent cardiomyocytes show disarray with interstitial fibrosis (Hematoxylin and Eosin stain, 200x)



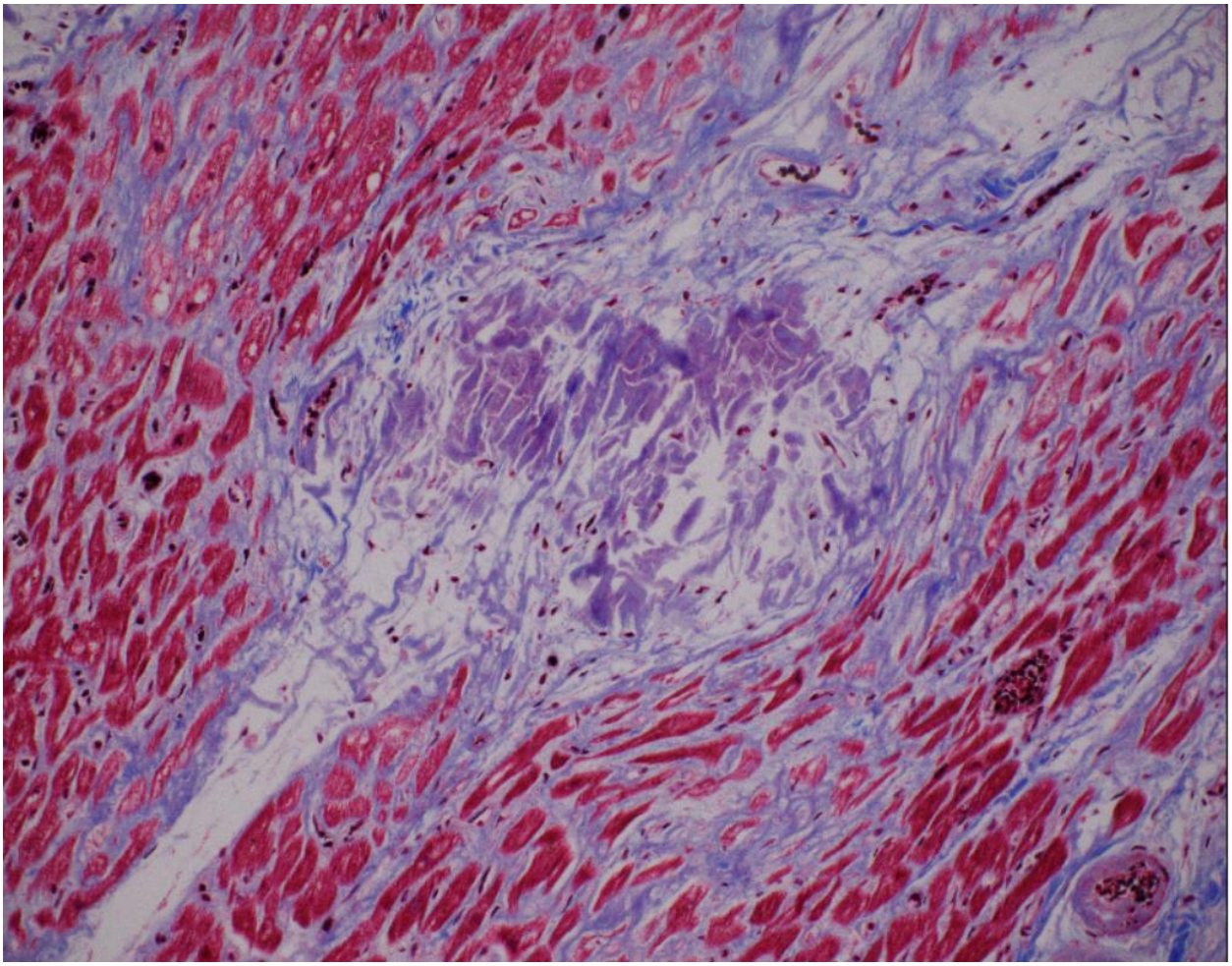
Amyloid deposition in cardiac tissue, showing accumulation of extracellular light eosinophilic, pale-pink, acellular, amorphous material with cracked appearance. (Hematoxylin and Eosin stain, 400x)



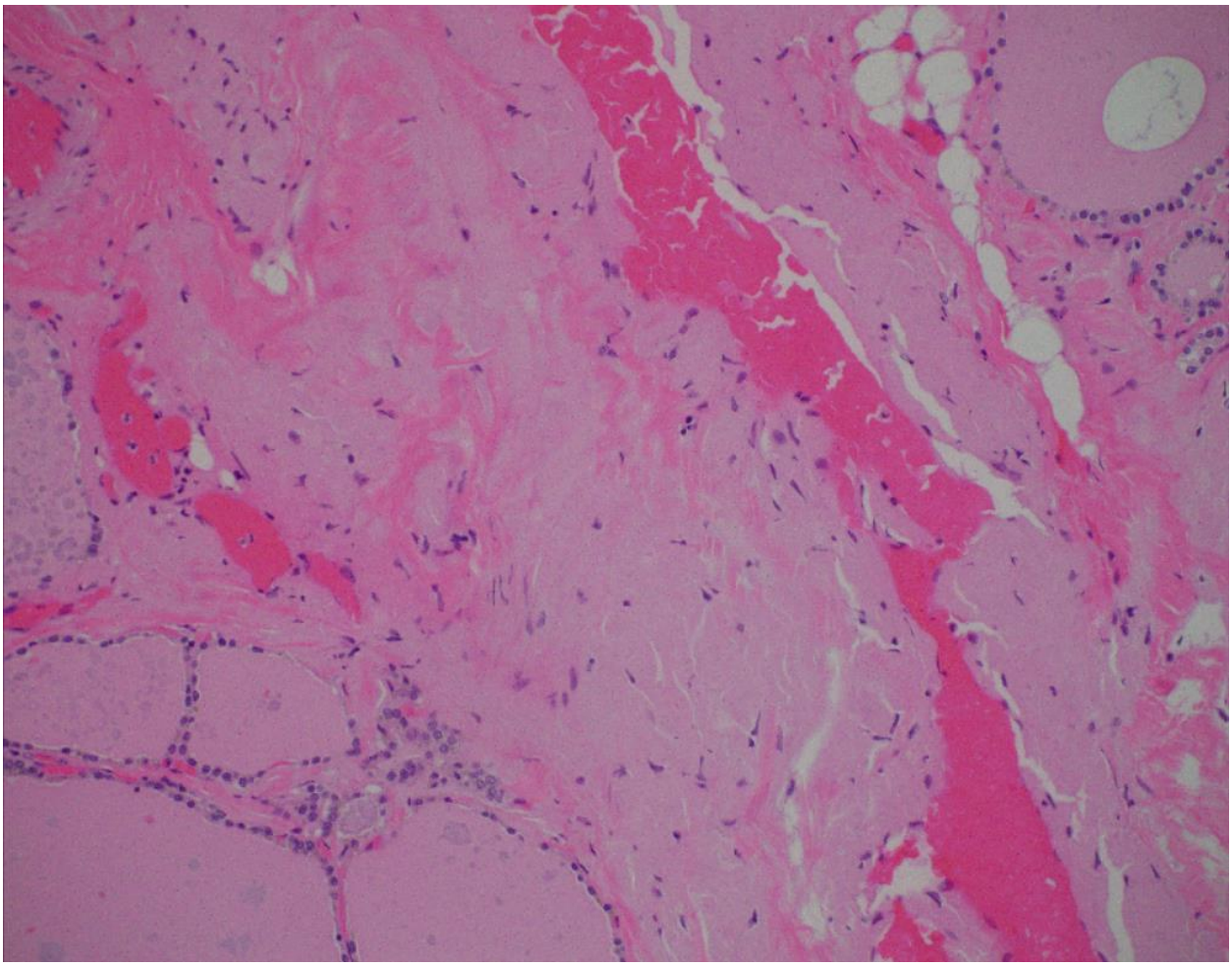
Congo Red staining of amyloid deposits in cardiac tissue showing accumulation of red-orange, salmon color, amorphous and acellular material (Congo Red, 200x)



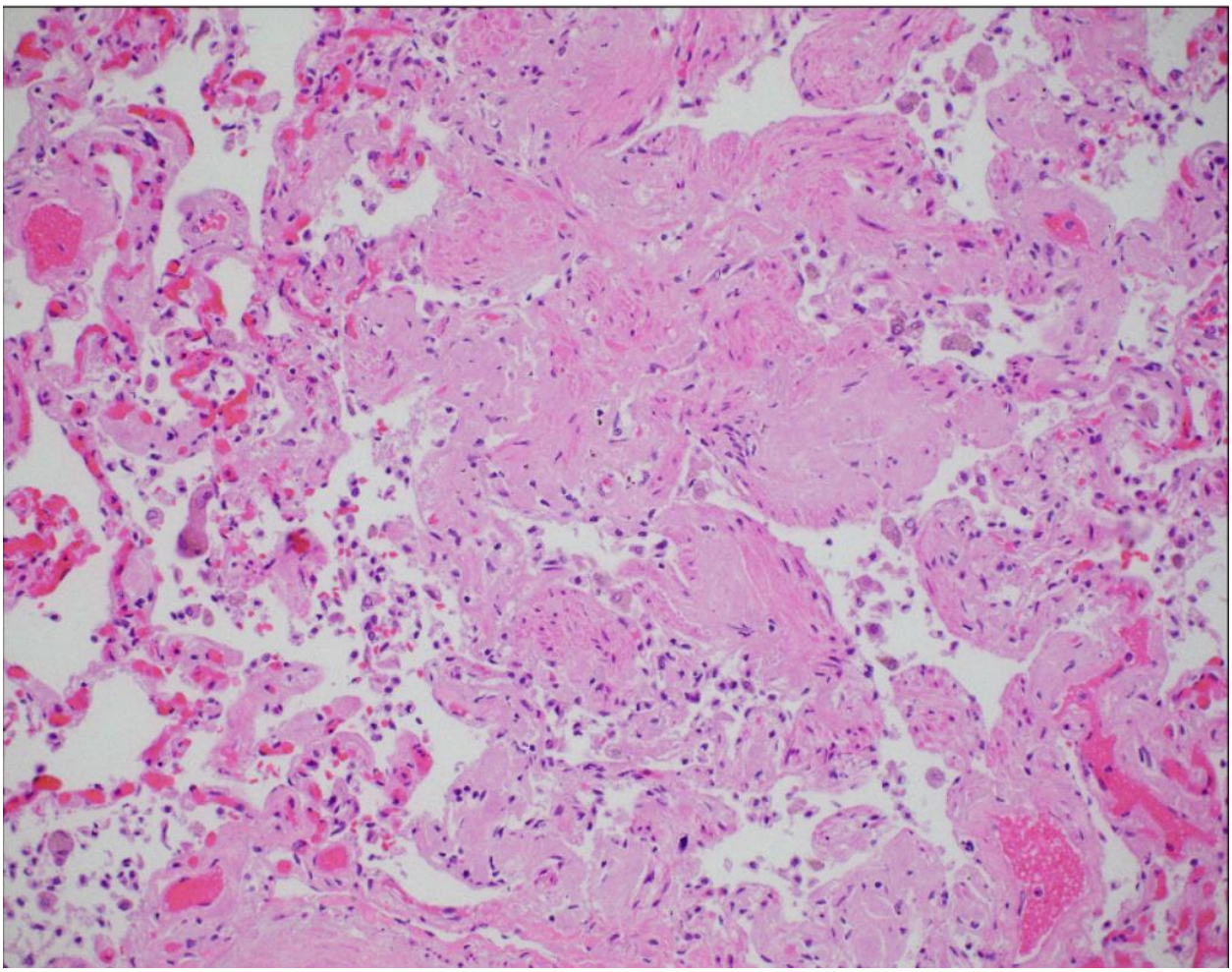
Congo Red staining of cardiac tissue viewed under polarized light shows yellow and apple-green birefringence, consistent with amyloid deposition. The white signal under polarized light corresponds to collagen of interstitial fibrosis. (Congo Red stain, polarized light, 200x)



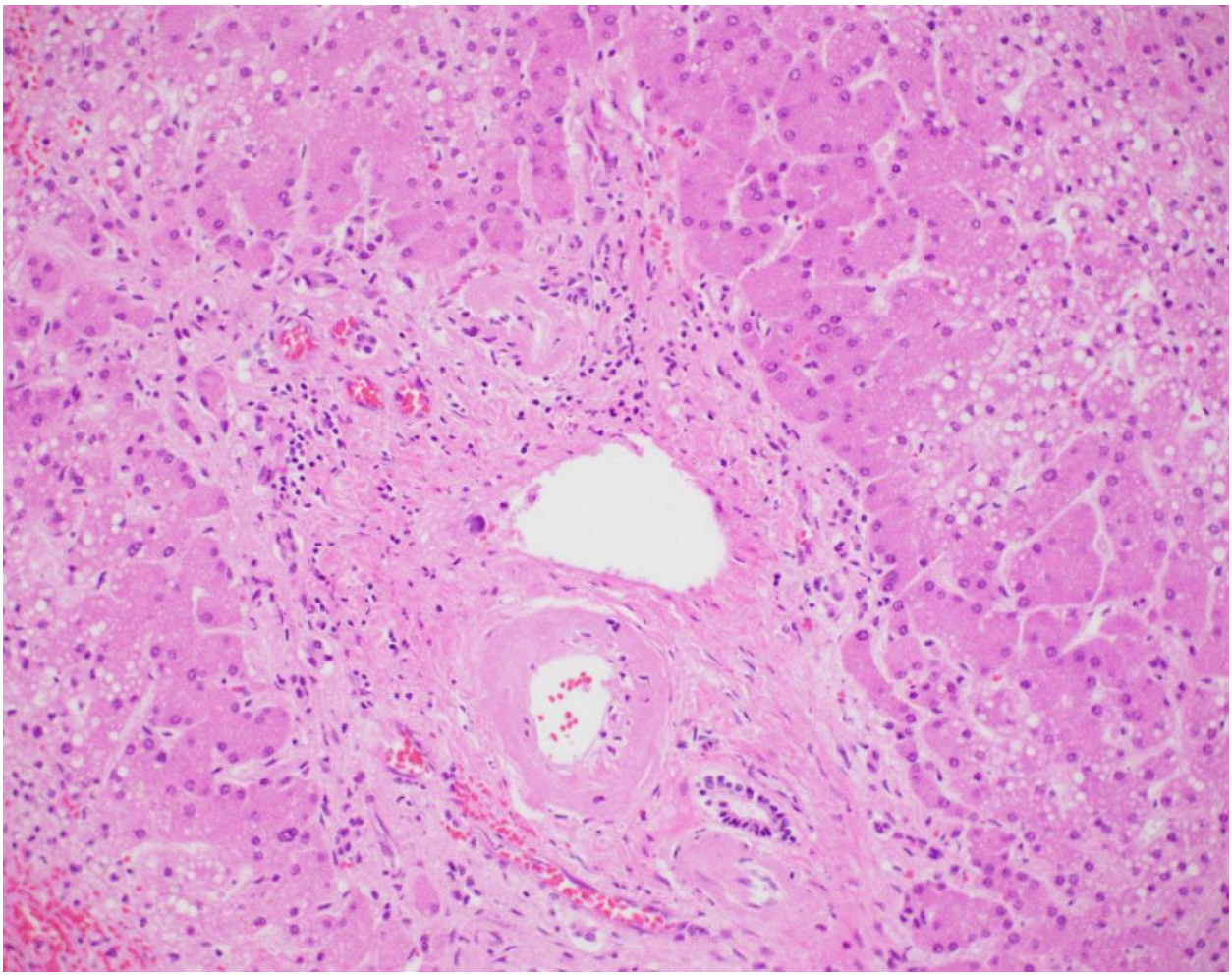
Trichrome staining of cardiac tissue shows purple-grey color amyloid deposits as compared with strong blue color of collagenous tissue. (Trichrome stain, 200x)



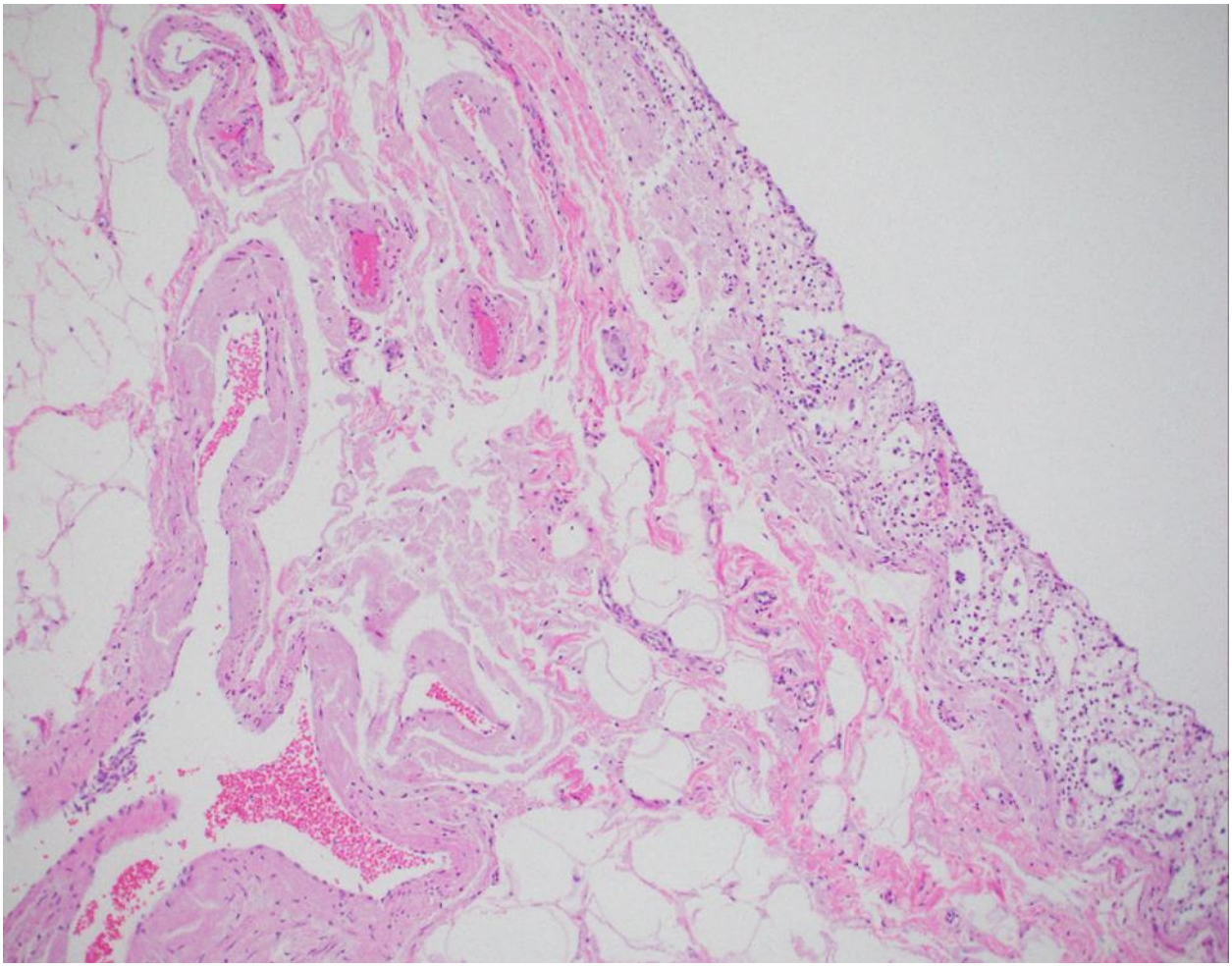
Amyloid deposition surrounding thyroid follicles. (Hematoxylin and Eosin stain, 200x)



Interstitial amyloid deposition in the lung (Hematoxylin and Eosin stain, 200x).



Vascular and perivascular amyloid deposition in the portal area of the liver (Hematoxylin and Eosin stain, 200x).



Amyloid deposition in the lamina propria of the colon (Hematoxylin and Eosin stain, 100x).

Other techniques for diagnosis:

LC-MS/MS: AL amyloidosis (immunoglobulin light chain, lamda) type

Differential diagnoses:

Hyalinized Collagen

Systemic Amyloidosis

Diagnosis:

Systemic AL Amyloidosis
- Amyloidosis involving heart, lungs, kidneys, thyroid, adrenals, spleen, gastrointestinal tract, blood vessels and urinary bladder wall
- Amyloid protein ID, LC MS/MS (performed at mayo clinic laboratories, MN): amyloidosis AL (lambda) type.

Discussion:

Systemic amyloidosis is an uncommon and devastating disorder in which misfolded proteins resistant to catabolic process deposit extracellularly in various tissues, leading to multi-organ damage and dysfunction (1, 2). More than 40 different proteins have been identified as amyloid precursors. Amyloid is composed of insoluble and degradation-resistant fibrillar proteins, which all have a similar structure forming the characteristic β pleated sheets (1, 2). The most common forms of systemic amyloid are light chain (AL) amyloid seen in plasma cell dyscrasia, AA amyloid associated with inflammatory condition and transthyretin (TTR) amyloid with wild-type transthyretin (ATTRwt) amyloidosis (senile systemic amyloidosis) associated with aging (1, 2). AL amyloidosis is characterized by a propensity for multi-organ involvement with heart and kidneys most commonly involved. Heart involvement dominates the clinical course and the outcome presenting as rapidly progressive congestive heart failure (1, 2).

Diagnosis of systemic amyloidosis requires clinical presentation as an amyloidosis syndrome with histopathology confirmation of amyloid deposits in tissues (1, 2). Congo Red staining is a standard method used to identify amyloid in tissues (1-3). Under polarized light microscopy, Congo Red positive extracellular deposits show yellow-apple green birefringence, consistent with amyloid. In nonpolarized light, amyloid deposits present as extracellular Red-orange, salmon color, amorphous and acellular material with characteristic cracking appearance in Congo Red stained section, whereas in Hematoxylin and Eosin stained section, amyloid appears pale-pink color. The location of amyloid deposits is often in vascular walls or perivascular areas. Amyloid should be distinguished from hyalinized collagen, which may appear similarly to amyloid on H&E stained section. Congo Red can nonspecifically bind collagen, fibrin, and elastin. However, characteristic binding of Congo Red to the β sheets of amyloid fibrils results in yellow and green exchangeable birefringence in polarized light when crossing the polarizer and analyzer, whereas other congophilic material like collagen and elastin are not birefringent while showing white signal in polarized light. In addition, in trichrome staining, amyloid deposits are purple-grey color whereas collagen/fibrotic tissue are strong blue color. Identification of amyloid with Congo Red staining is challenging because of multiple interfering factors including staining and processing protocol, thickness of the section, light source/intensity, and microscope settings, which may cause false-positive or false-negative results (3-5). Other methods including immunohistochemical staining, fluorescence microscopy and (immune)electron microscopy have also been used for detecting amyloid, but all have limitations and require optimization (6, 7, 8). Laser microdissection of amyloid fibril followed by chromatography-tandem mass spectrometry (LC-MS/MS) is now the definitive method for amyloid typing and confirmation (8).

Early detection and typing of amyloid deposits are very important for effective treatment of systemic amyloidosis. Fat pad aspiration is the initial step to detect amyloidosis in clinical suspicious patients. If it fails to show amyloid deposition and suspicion remains high, a biopsy of the involved organ should be pursued. Cardiac amyloidosis contributes significantly to morbidity and mortality in systemic amyloidosis patients. Early detection and typing of amyloidosis using standard Congo Red staining and trichrome staining followed by LC-MS/MS is essential for the prognosis and management of systemic amyloidosis.

References:

1. Muchtar E, Dispenzieri A, Magen H, Grogan M, Mauermann M, McPhail ED, Kurtin PJ, Leung N, Buadi FK, Dingli D, Kumar SK, Gertz MA. Systemic amyloidosis from A (AA) to T (ATTR): a review. J Intern Med. 2021 Mar;289(3):268-292. doi: 10.1111/joim.13169. PMID: 32929754

2. Jamal F, Rosenzweig M. Amyloidosis with Cardiac Involvement: Identification, Characterization, and Management. Curr Hematol Malig Rep. 2021 Aug;16(4):357-366. doi: 10.1007/s11899-021-00626-4. PMID: 34106429

3. Yakupova EI, Bobyleva LG, Vikhlyantsev IM, Bobylev AG. Congo Red and amyloids: history and relationship. Biosci Rep. 2019 Jan 15;39(1):BSR20181415. doi: 10.1042/BSR20181415. PMID: 30567726

4. El-Meanawy A, Mueller C, Iczkowski KA. Improving sensitivity of amyloid detection by Congo Red stain by using polarizing microscope and avoiding pitfalls. Diagn Pathol. 2019 Jun 14;14(1):57. doi: 10.1186/s13000-019-0822-4.PMID: 31200733

5. Howie AJ, Brewer DB, Howell D, Jones AP. Physical basis of colors seen in Congo Red-stained amyloid in polarized light. Lab Invest. 2008 Mar;88(3):232-42. doi: 10.1038/labinvest.3700714. PMID: 18166974

6. Lee AYS, Bayly A, Lin MW. Evaluation of Polarized Light and Fluorescence Microscopy of Congo Red Stain in the Diagnosis of Renal Amyloidosis. Lab Med. 2021 Nov 2;52(6):574-577. doi: 10.1093/labmed/lmab022.PMID: 33929031

7. Schönland SO, Hegenbart U, Bochtler T, Mangatter A, Hansberg M, Ho AD, Lohse P, Röcken C. Immunohistochemistry in the classification of systemic forms of amyloidosis: a systematic investigation of 117 patients. Blood. 2012 Jan 12;119(2):488-93. doi: 10.1182/blood-2011-06-358507. PMID: 22106346

8. Goldis R, Kaplan B, Kukuy OL, Arad M, Magen H, Shavit-Stein E, Dori A, Livneh A. Diagnostic Challenges and Solutions in Systemic Amyloidosis. Int J Mol Sci. 2023 Feb 28;24(5):4655. doi: 10.3390/ijms24054655. PMID: 36902083