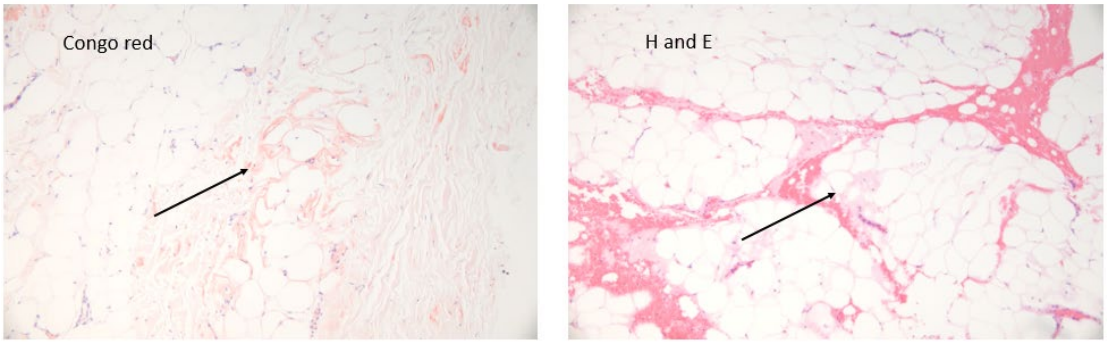
COLLEGE of AMERICAN PATHOLOGISTS

Laboratory Workup of Amyloidosis

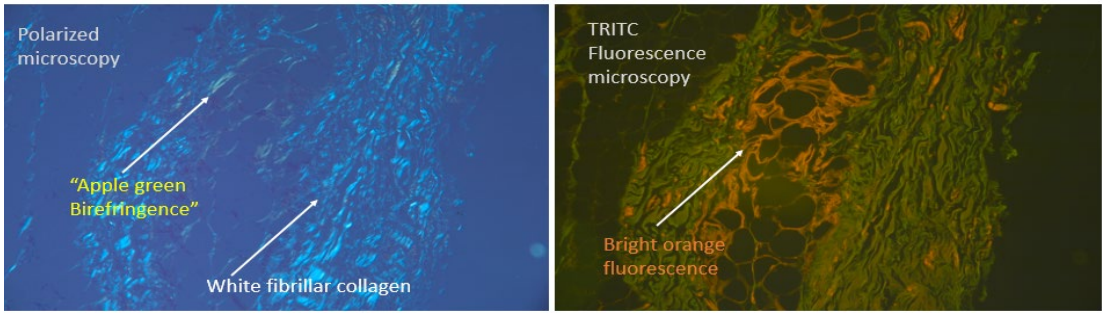
Case Studies

EXAMPLE CASE 1

A 73-year-old male with longstanding type 1 diabetes mellitus presented to his physician complaining of fatigue, dizziness, numbness in his feet, and diarrhea. Laboratory studies demonstrated elevated kappa free light chains and a kappa monoclonal gammopathy of undetermined significance. A fat aspirate showed Congo red-positive amyloid deposits, and a bone marrow exam demonstrated 5% monoclonal kappa plasma cells.



Positive Fat Pad Biopsy. H&E with pale pink material (right) that stains positively with Congo red (left). Image courtesy Billie S. Fyfe, MD.



Positive Fat Pad Biopsy – Congo Red Microscopy Techniques. Under polarized light, the Congo red positive deposits show typical birefringence (left), in contrast to the white birefringence of collagen in the fat pad. Under tetramethylrhodamine isothiocyanate (TRITC) filter fluorescence, the amyloid deposits appear a prominent bright orange. Image courtesy Billie S. Fyfe, MD.

At this point the working diagnosis was systemic AL amyloidosis. Typing of the amyloidogenic fat pad specimen by LC-MS/MS (mass spectrometry) demonstrated AIns (insulin) amyloidosis. Since AIns is a localized process without systemic symptoms, this did not explain the patient's fatigue, dizziness, numbness, and diarrhea, so an endomyocardial (target organ) biopsy was performed. The endomyocardial biopsy contained Congo red-positive amyloid deposits, which were shown to be of ATTR type by LC-MS/MS (mass spectrometry). An amino acid abnormality indicative of hereditary ATTR (ATTRv) was not identified by LC-MS/MS, nor was an ATTR mutation identified in subsequent peripheral blood sequencing studies. Final diagnoses in this case: 1) systemic ATTRwt amyloidosis; 2) localized AIns amyloidosis; and 3) monoclonal gammopathy of undetermined significance.

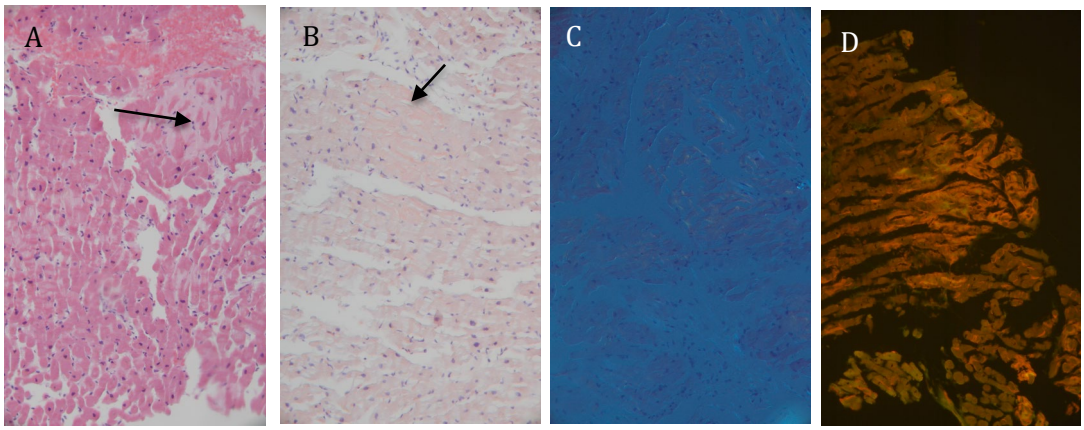
This case illustrates several points: 1) The presence of monoclonal gammopathy of undetermined significance does not guarantee systemic AL-type amyloidosis; 2) a patient may have more than one type of amyloidosis; 3) amyloidosis may be systemic or localized and the fibril type may help distinguish this (AIns is a localized and clinically inconsequential form of amyloidosis); and 4) fat pad specimens are easily accessible with minimal

complications, but sensitivity for detection of amyloid varies depending on the amyloid type (up to 80% for AL amyloidosis; only 15% in ATTRwt amyloidosis)[1-3]

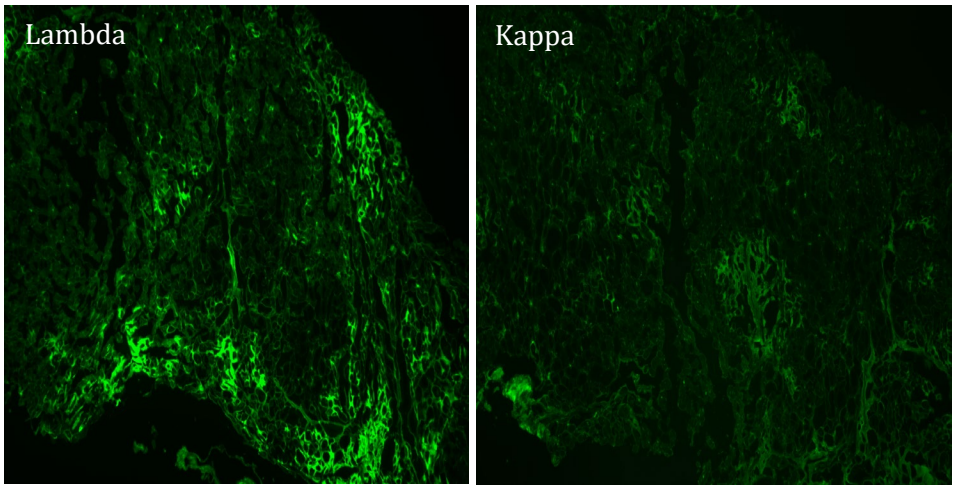
EXAMPLE CASE 2

A 70-year-old-man with type 2 diabetes mellitus and hypertension was recently diagnosed with multiple myeloma (IgG lambda) after his nephrologist ordered urine protein electrophoresis which showed faint IgG lambda bands. Subsequent bone marrow biopsy positive for plasma cell neoplasm involving 30-40% of the marrow. Bone marrow biopsy Congo red stain was negative for amyloid deposits.

The patient underwent stem cell transplantation for the multiple myeloma. Four months later he presented with congestive heart failure. He also has a remote history of bilateral carpal tunnel surgery. EKG and echocardiogram were suggestive of cardiac amyloidosis with discrepancy between voltage and hypertrophy. A cardiac pyrophosphate (PYP) scan was performed and read as not suggestive of ATTR amyloid. The patient underwent endomyocardial biopsy for evaluation for cardiac amyloidosis.



Endomyocardial biopsy: A) pale pink “waxy” interstitial deposit material (arrow) (H&E x100), B) Subtle salmon-colored staining of the deposit material by Congo red (x100), C) Polarized microscopy showing typical birefringence of amyloid (Congo red x100), D) TRITC fluorescence showing prominent orange fluorescence of amyloid (Congo red x100). Image courtesy Billie S. Fyfe, MD.



Endomyocardial biopsy: Immunofluorescence light chain staining showing apparent lambda dominant pattern (although kappa is not entirely negative). Image courtesy Billie S. Fyfe, MD.

Based on light chain immunofluorescence staining on the endomyocardial biopsy, AL Lambda amyloidosis seemed most likely, but the paraffin tissue block was sent for fibril typic by mass spectrometry. Results of that fibril typing showed the cardiac amyloid deposits to be ATTR type.

This case illustrates several points: 1) Newer cardiac imaging techniques are not replacing ALL endomyocardial biopsies for amyloid evaluation. The current clinical setting of an older patient with MGUS or multiple myeloma and

equivocal cardiac PYP imaging is now a common indication for endomyocardial biopsy. 2) In situations of circulating light chains there can be some nonspecific light chain staining identified on immunofluorescence or immunohistochemistry that does not relate directly to the amyloid fibril but to the circulating monoclonal protein. Thus, fibril type confirmation is very important to determine the validity of staining results as well as to potentially identify combined amyloid types. 3) Pathologist should be alerted to the noted increased risk for identifying systemic amyloidosis in patients with prior carpal tunnel syndrome, bicep tendon rupture, and lumbar stenosis. Such clinical information should increase suspicion and evaluation for amyloid deposits in any type of surgical pathology specimen.

1. Fine NM, Arruda-Olson AM, Dispenzieri A et al. Yield of noncardiac biopsy for the diagnosis of transthyretin cardiac amyloidosis. *Am J Cardiol*. 2014;113(10):1723-1727. doi:10.1016/j.amjcard.2014.02.030.
2. Miller DV FB, Bhatt KN, et al. Laboratory workup of amyloidosis *Archives of Pathology and Laboratory Medicine*. 2025. doi:10.5858/arpa.2025-0275-CP.
3. Quarta CC, Gonzalez-Lopez E, Gilbertson JA et al. Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis. *Eur Heart J*. 2017;38(24):1905-1908. doi:10.1093/eurheartj/ehx047.