An Organ System–Based Approach to Differential Diagnosis of Amyloid Type in Surgical Pathology

Gabriel Giannini, MD; Cynthia C. Nast, MD

- **Context.**—Amyloidosis is an uncommon but important entity. A protein-based classification of amyloidosis defines the underlying disease process, directing clinical management and providing prognostic information. However, in routine surgical pathology there often is no attempt to classify amyloid other than staining to determine light chain–associated amyloidosis. Systemic and localized amyloidosis vary with respect to frequency of organ involvement by different amyloid types, and most amyloid proteins have commercial antibodies available for identification.

  - **Objective.**—To provide a guide for the likelihood of amyloid type by organ system.

- **Data Sources.**—Literature review based on PubMed searches containing the word amyloid, specifically addressing the prevalence and significance of amyloid proteins in each organ system other than the brain, and the authors’ practice experience.

  - **Conclusions.**—In patients with amyloidosis, determination of the responsible protein is critical for appropriate patient care. In large subspecialty practices and reference laboratories with experience in using and analyzing relevant immunohistochemistry, most amyloid proteins can be identified with an organ-specific algorithm. Referring to an organ-based algorithm may be helpful in providing clinicians with a more specific differential diagnosis regarding amyloid type to help guide clinical evaluation and treatment. When the protein cannot be characterized, mass spectrometry can be performed to definitively classify the amyloid type.


Amyloidosis is defined as tissue deposition of protein fibrils that form insoluble β-sheet sheets. It has a reported prevalence of 20 per million with an incidence of 10 to 13 per million. While not common, it can be a devastating disease. In tissue sections, amyloid appears as a glassy, acellular, amorphous pale eosinophilic material with hematoxylin-eosin staining and is detectable by Congo red stain. The gold standard for the identification of amyloid is the characteristic “apple green” birefringence of polarized Congo red–stained tissue. However, it should be noted that there are reports of Congo red–negative amyloid requiring thioflavin T or crystal violet for diagnosis, although the latter method may be less sensitive. Amyloid demonstrated by crystal violet displays a metachromatic magenta or pink-violet color. Thioflavin T helps highlight amyloid with enhanced fluorescence emission at 480 nm, when excited at 450 nm.

To date, 36 proteins have been recognized as causative agents in systemic and/or localized amyloidosis. Classification of the amyloid protein is critical for diagnosis of the underlying disease process, which drives appropriate treatment and allows for a more accurate prognosis. Prognosis also may depend on amyloid load and density, which should be included with amyloid reporting. Amyloid proteins have varying propensities for organ system involvement, and the pattern of organ deposition may suggest the amyloidogenetic protein involved. Therefore, knowing the amyloid types most often found in specific organ systems allows the pathologist to provide a more specific differential diagnosis, potentially guiding the patient’s clinical evaluation. Exclusive of the brain, which will not be covered in this review, the 5 most frequent classes of amyloid proteins account for up to 95% of cases (Table 1). For cases that cannot be classified definitively with immunohistochemistry (IHC) in an experienced large subspecialty practice or reference laboratory, the involved protein can be identified by mass spectrometry although at increased cost, potentially longer turnaround time, and with loss of tissue. The authors’ experience in using IHC for amyloid typing is demonstrated in organ-specific examples provided in the Approach and Proposed Algorithms section below.

**TYPES OF AMYLOID**

The 5 most common types of amyloid (light chain, transthyretin, serum amyloid A, β2-microglobulin, and leukocyte chemotactic factor-2) are discussed below, and together comprise approximately 95% of all non-central nervous system amyloid cases. A brief mention of the less rare forms of amyloid follows.

**Light Chain Amyloid**

Light chain (AL) amyloidosis, often termed primary amyloidosis, comprises 78% of amyloid cases and is a
disorder of monoclonal plasma cell proliferation resulting in deposition of the abnormal paraprotein as amyloid. It often is associated with myeloma, monoclonal gammopathy of unknown or of renal significance, or Waldenstrom macro-globulinemia. The average age at onset is 58 years, with a 1.5:1 male to female predominance, and a $k$ to $j$ ratio of 3.8:1.12 Symptoms are nonspecific, including weight loss, fatigue, and purpura. Other symptoms are dependent on which organs are involved and can include nephrotic syndrome, restrictive cardiomyopathy, peripheral neuropathy, hepatomegaly with elevated liver enzymes, purpura, or bleeding.13 The incidence of AL amyloidosis is estimated to be 8 to 9/1 000 000 person-years14 or 4.5/100 000.15 Of patients with myeloma, 15% will have clinical AL amyloidosis and up to 30% can have subclinical amyloid deposits.16 Conversely, 20% of patients with AL amyloidosis have myeloma and the remainder have other B-cell disorders.15 In a study by Matsuda et al,12 AL amyloid was found to affect many organs, most frequently the kidney in 109 of 202 cases (54%), heart in 50 of 202 (24.8%), peripheral nerves in 21 of 202 (10.4%), and liver in 16 of 202 (7.9%). Treatment for AL amyloidosis requires treatment of the underlying plasma cell dyscrasia.17

### Transthyretin Amyloid

Transthyretin (TTR) is a tetrameric protein on chromosome 18 that can fold into $\beta$ sheets and is synthesized and secreted into the blood by the liver. Transthyretin amyloid (ATTR) is found in 13% to 17% of amyloid cases owing to its prevalence in the heart and lung. It is divided into hereditary

<table>
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<th>Protein</th>
<th>Abbreviation</th>
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<th>Localization</th>
<th>IHC Available Commercially</th>
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Abbreviations: Ig, immunoglobulin; IHC, immunohistochemistry antibody; L, localized; S, systemic.

a Some types of amyloid are composed of proteins from both wild-type (No) and mutant (Yes) genes.

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IHC Classification of Amyloid—Giannini & Nast
Serum Amyloid A

Serum amyloid A (AA) amyloidosis accounts for 6% of amyloid cases due to deposition of AA protein, an acute phase reactant made by the liver, and has been called secondary amyloidosis. It has been estimated to be the cause of up to 45% of all generalized amyloid cases. AA amyloidosis typically is associated with chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and chronic infections, and other conditions including familial Mediterranean fever and heroin skin popping; however, in up to 6% of cases no underlying cause is found. It most frequently can be found in the kidneys, gastrointestinal (GI) tract, spleen, liver, and autonomic nerves and is best managed by treating the underlying disease process. The prevalence of AA amyloid has decreased relative to AL amyloid in developed countries, likely due to earlier diagnosis and treatment of infectious agents, which can be the dominant primary etiology in less developed or tropical countries.

β2-Microglobulin Amyloid

β2-microglobulin (β2M) is a component of the major histocompatibility complex that is present on all cells. It is normally cleared by glomerular filtration with later reabsorption and catabolism in proximal tubules. In the setting of chronic or end-stage kidney disease, there is reduced filtration of β2M, which may accumulate in different organs and form amyloid (Aβ2M). The incidence of dialysis-related amyloidosis has decreased with the increased use of high-flux dialysis membranes. However, histologic studies have shown that Aβ2M amyloidosis is more common than clinically suspected, occurring in 90% of patients after 7 years of dialysis, developing more quickly in the elderly, and associated with hemodialysis and peritoneal dialysis, although it may occur with renal dysfunction before initiation of dialysis. While there typically is osteoarticular amyloid deposition, in this patient population Aβ2M amyloid has been identified in many organ systems. Kidney transplant can result in relief of arthralgias, although likely due to corticosteroid treatment. Aβ2M may be detected up to 2 decades after a successful renal transplant. Similar to ATTRm, Aβ2M amyloidosis may be hereditary with an autosomal dominant Asp76Asn variant Aβ2M, which can cause a slowly progressive autonomic neuropathy and GI symptoms.

Leukocyte Chemotactic Factor-2 Amyloid

Initially, leukocyte chemotactic factor-2 (LECT2) was thought to result from only the wild-type protein without associated genetic abnormalities; however, more recently it was found to be associated with a polymorphism resulting in substitution of isoleucine for valine at position 40 in the mature protein. LECT2 amyloid (ALECT2) is either the second or third most common cause of renal amyloidosis, depending on the patient population. It is the second most common (25%) cause of hepatic amyloidosis and can also involve the spleen, pulmonary alveoli and septa, and adrenal gland. There is a prevalence of 0.7% in the general population that reaches 4.25% in people of Hispanic descent. There is no specific treatment, but kidney disease progression tends to be slow, resulting in a mean rate of glomerular filtration rate loss of 4.2 mL/min/yr and a median estimated patient survival from diagnosis greater than 15 years.

Other Amyloid Types

These are discussed in a recent review. While there are antibodies available commercially for many of these amyloid types, their rarity precludes cost effectiveness of IHC validation and maintaining the antibody in the clinical laboratory. The less rare forms include apolipoprotein A and C variants (AApo) amyloid, caused by deposition of one of the apolipoprotein family of proteins, which are encoded on chromosome 11. There are sporadic and familial types associated with apolipoproteins AI, AI, AIV, CII, and CIII, which can be deposited in the heart, liver, kidneys, skin, larynx, and testes, sometimes with specific localizations in the organs depending on the variant. Gelsolin (AGel) amyloidosis is systemic and hereditary, typically presenting as an autosomal dominant polyneuropathy syndrome. Lysozyme (ALys) amyloidosis is a consequence of 1 of 7 mutations in the lysozyme enzyme, and may be found in many organ systems but is predominantly nephropathic or involves the GI tract. Fibrinogen Aα (AFib) is an autosomal dominant systemic amyloidosis caused by mutations in the fibrinogen A-chain gene on chromosome 4. It preferentially involves renal glomeruli and clinically presents with proteinuria, hypertension, and azotemia. Heavy chain (AH) amyloid is rare with few reported cases in the literature, may occur with or without accompanying AL amyloidosis, and usually involves immunoglobulin (Ig) G or IgA.

APPRAOCH AND PROPOSED ALGORITHM

Excluding the brain, the most common organ systems affected by clinically significant amyloid deposition include the heart, kidney, GI tract, liver, lungs, peripheral nerves, and bone/joints/carpal tunnel. The common amyloid protein classes for which IHC antibodies are available include light chains (k and λ, AL), AA protein, TTR, LECT2, and Aβ2M.
Abbreviations: AA, serum amyloid A; AANF, atrial natriuretic factor; ALECT2, leukocyte chemotactic factor-2; ALys, lysozyme; ApoA1, apolipoprotein AI; ApoAII, apolipoprotein AII; ApoAIV, apolipoprotein AIV; ApoCII, apolipoprotein CII; ApoCIII, apolipoprotein CIII; ATR, transthyretin; 2M, 2-microglobulin; AFib, fibrinogen A; AGel, gelsolin; AL, light chain; ATTR, transthyretin.

These proteins may be wild type or, in select cases, associated with acquired or hereditary genetic mutations resulting in disease, and additionally may be systemic or localized (Table 1). Other less common amyloid proteins either are so uncommon as to not warrant keeping them current in a clinical IHC laboratory or do not have antibodies available commercially. Different organ systems have a propensity for deposition of specific amyloid proteins with the exception of paraproteins, which may be found in virtually every organ. Below is a summary of the amyloid types and the organs in which they most frequently occur, allowing for targeted characterization of amyloid in each location (Table 2).

Heart

(Common: AL, ATTR; less common: AA; rare: AApors, AApoAIV, AFib, Aβ2M, AANF [atrial natriuretic factor])

Cardiac amyloidosis typically presents with symptoms of right-sided heart failure. Amyloid fibrils infiltrate the ventricles, resulting in stiffening and thickening. This causes decreased compliance and increased pressure, which results in diastolic dysfunction. Patients present with dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, abdominal distension, and lower extremity edema. While the heart is a target of several types of amyloid, more than 95% of cases are due to AL and ATTR. It has been estimated that 20% to 35% of those with a light-chain paraprotein develop amyloid, while between 50% and 90% of those with AL amyloid have cardiac involvement, making this the most common form found in the heart. The pattern of AL amyloid deposition is usually subendocardial and diffuse in a reticular/pericellular pattern. ATTR accounts for 18% of cases of cardiac amyloid typically in a patchy distribution. ATTRwt, also known as senile amyloidosis, occurs in older adults, usually after the sixth decade of life. Up to 25% to 36% of those older than 80 years are at risk of developing cardiac ATTRwt, which is likely underdiagnosed. Autopsy studies have identified cardiac ATTRwt in 25% of patients 85 years and older, and in 19% of those with heart failure and preserved ejection fractions. ATTRm disproportionally affects African Americans and, while much less prevalent than ATTRwt, is the most common hereditary form of cardiac amyloidosis in the United States. Other rare forms of cardiac amyloid have been reported.

Kidney

(Common: AL, AA, ALECT2 in susceptible populations; uncommon: ATTR; rare: AFib, AApors, AApoAIV, AApoCII, AApoCIII, AGel, AANF)

The prevalence and location of renal involvement vary with the amyloid type, presenting as proteinuria with glomerular involvement and reduced renal function with tubulointerstitial or vascular amyloid deposition. In the glomerulus, amyloid typically first deposits in mesangial regions then extends to the capillaries and eventually replaces the entire glomerulus. When glomeruli are involved, there often is amyloid in the intrarenal vasculature. In a large clinicopathologic series of 474 renal amyloidosis cases, AL was the most common type found in 407 of 474 (85.9%), followed by AA in 33 of 474 (7.0%). A smaller study of 231 renal biopsies showed similar results. A significant minority of renal amyloid cases are caused by LECT2 amyloid seen in 13 of 474 cases (2.7%), a percentage supported in a separate study by Larsen and colleagues. However, as ALECT2 is common among those of Hispanic or Egyptian descent, this amyloid type may be more prevalent than AA amyloid in these populations. The remaining cases were composed of AFib in 6 of 474 (1.3%), and other rare amyloid types.

AL amyloid will deposit in any renal structure but tends to be vasculotropic in early stages. Certain other amyloid types have a propensity for accumulating in specific renal compartments, providing a clue as to their composition. AA amyloid favors glomeruli and vessels, but also can deposit in the tubulointerstitium. AFib is almost exclusively glomerular. ALECT2 and ATTR tend to occur in the renal tubulointerstitium, with glomerular and vascular involvement to a much lesser extent in ALECT2 and minimally with ATTR. ApoAIV amyloid has a propensity for medullary interstitial deposition, so a cortical biopsy may not contain the amyloid. Therefore, the location of the amyloid may support staining for specific amyloid types even if they are not common or the patient’s ethnicity is not known.

Renal cortical interstitial amyloid usually is of the LECT2 or TTR type. Figure 1, A, shows a biopsy with prominently cortical interstitial involvement by amyloidosis with minor infiltration of glomerular mesangial areas from a patient with moderate to severe hypertension, diabetes, monoclonal gammopathy, stage 4 chronic kidney disease for 6 years, and an IgM paraprotein on serum and urine protein electro-
phoresis. No amyloid staining for IgM, or κ or λ light chains, is seen on immunofluorescence (Figure 1, A). Immunohistochemistry for both light chains, AA amyloid, and ATTR and LECT2 (due to the predominant interstitial location of the amyloid) stained only for LECT2 by IHC (Figure 1, B). The patient has been followed up for a monoclonal gammopathy of unknown significance and has not required treatment for plasma cell dyscrasia.

Gastrointestinal Tract

(Common: AL, AA, ATTR; less common: Aβ2M; rare: AApoAI, ALys)

In the GI tract, amyloid may deposit from the mouth to the anus. Resulting symptoms range from macroglossia to those found with inflammatory or other bowel diseases.51,52 The most common forms of GI amyloidosis are AL, ATTR, and AA.53 Freudenthaler et al54 examined amyloid in 542
biopsy specimens from all areas of the GI tract and identified AL in 360 of 542 (66.4%), ATTR in 88 of 542 (16.2%), AA in 58 of 542 (10.7%), AApoAI in 4 of 542 (0.7%), and ALys in 4 of 542 (0.7%); Aβ2M was not tested in their study.54 There are few reports of Aβ2M amyloidosis in colons of patients receiving dialysis and in the setting of the Asp76Asn Aβ2M variant.28,55 Within the GI tract, there are different sites of deposition dependent on the type of amyloid present. AL tends to be found in the submucosal layer and/or muscularis propria as a nodule or mass, while ATTR and Aβ2M both occur around and within vessels and nerves. AA accumulates in the lamina propria mucosae and submucosal layer in a macular or perivascular form.56,57

Figure 2 shows the amyloid pattern in a GI biopsy from a patient with a remote history of breast cancer who was diagnosed with systemic lupus erythematosus and underwent positron emission tomography/computed tomography scan for GI symptoms that showed intestinal inflammation. Figure 2, A, demonstrates submucosal perivascular amyloidosis in the small intestinal biopsies, which prompted IHC for ATTR and Aβ2M; the location and presence of collagen vascular disease triggered AA testing, and staining was done for both light chains owing to the patient’s age of 63 years. AA amyloid was confirmed, thus obviating the need for additional workup other than confirming the lack of an abnormal paraprotein serologically (Figure 2, B).

Liver

(Common: AL, ATTR, ALECT2; uncommon to rare: AApoAI, AA, ALys, AFib, Aβ2M)

Hepatic amyloidosis can present with a variety of symptoms, ranging from hepatomegaly with mildly elevated levels on liver function tests to portal hypertension and hepatic failure.57 Hepatic amyloidosis is usually characterized by deposition in the liver parenchyma along the sinusoids, within the spaces of Disse, or within the blood vessel walls.58 In the setting of systemic amyloidosis, 70% will have liver involvement although it may be asymptomatic.59 In a series of 130 cases of hepatic amyloid, AL was the most frequent accounting for 81 of 130 (62%) followed by ALECT2 in 32 of 130 (25%), and AApoAI, AA, ATTR, and ALys constituting the remainder.31 In a study of 70 cases of hepatic amyloid, AL was the most commonly identified in 41 of 70 (59%), followed by ATTR in 15 of 70 (22%), with the remainder composed of AFib in 3 of 70 (4%), AA in 3 of 70 (4%), ALECT2 in 3 of 70 (4%), and AApoAI in 2 of 70 (3%).60 AL deposits occur with comparable frequency in the portal tracts, sinusoids, and blood vessels in a predominantly linear pattern. ATTR, AFib, and AA are found in a linear pattern of deposition in the sinusoids and vasculature. All ALECT2 deposits show a more amorphous and globular pattern in the sinusoids and portal tracts, while AApoAI can be linear in the portal tracts and vasculature.60

Therefore, similar to the kidney, the pattern and location of deposition in the liver may point to a particular amyloid type.

Figure 3, A, is a liver biopsy specimen demonstrating amyloid deposition in a linear sinusoidal pattern from a patient post lobectomy for a lung carcinoma who presented with right upper quadrant abdominal pain and scleral icterus, and then developed fatigue, low-grade fevers, and worsening jaundice. Figure 3, B, shows positive ATTR on IHC, demonstrating the value of using the deposition pattern and applying an algorithm for amyloid assessment.

Lung

(Common: AL, ATTR, AA; rare: ALECT2, Aβ2M)

Symptomatic pulmonary amyloidosis is rare but can be a significant problem in systemic or organ-limited disease. In contrast to the clinical findings, autopsy studies have shown 58% to 92% lung involvement in patients with systemic amyloidosis, where it usually is an incidental finding.61 AL amyloidosis is found in up to 85% of symptomatic pulmonary involvement usually with systemic disease. ATTRm and ATTRwt are found in fewer than 15% of symptomatic patients, although the lung is second only to the heart with regard to ATTR deposition. AA has an even lower incidence61,62 and there are single case reports of pulmonary ALECT263 and Aβ2M.64 Pulmonary amyloid can have 3 distinct histologic patterns. The diffuse alveolar-septal type usually is associated with systemic AL amyloidosis and very infrequently with AA, ATTRwt, and ATTRm amyloidosis.65 The nodular pulmonary type is typically asymptomatic AL or mixed AL/AH type but rarely may be AA or ATTR.66-68 Tracheobronchial amyloidosis is usually AL or AA amyloidosis and is often symptomatic owing to stenosis.

There is considerable overlap of amyloid type in the alveolar-sinusoidal lung pattern of deposition. The specimen in Figure 4 is derived from a lung biopsy performed on a patient with a family history of interstitial pulmonary fibrosis for whom lung imaging showed micronodular

Figure 4. Example of amyloid in a lung biopsy specimen showing (A) focal Congo red–positive amyloid with an alveolar-septal pattern of deposition with (B) positive staining for k light chain and (C) negative staining for κ light chain (original magnification ×400 [A through C]).
Amyloid may deposit in any organ system, particularly in AL amyloidosis. Additionally, localized amyloid may be found without a systemic distribution, which may or may not be clinically significant depending on the extent of associated organ dysfunction. Localized amyloidosis is particularly common in seminal vesicles, possibly composed of a locally synthesized amyloidogenic protein. When amyloid is found in other locations such as the adrenal gland, spleen, bladder, female reproductive tract, and thyroid, assessment for AL, AA, and ATTR is warranted, as a significant underlying systemic disease process may be identified.

**CAVEATS OF IHC STAINING FOR AMYLOID TYPES**

Available antibodies for IHC staining may identify both mutant and wild-type proteins for amyloid types where both can occur. Therefore, if it is important to differentiate these, genetic testing should be performed. Antibodies used to identify AL amyloidosis are directed against epitopes that may be truncated or absent in the abnormal light chain; therefore, it is possible that AL amyloid will have negative staining. If AL amyloidosis is suspected but the IHC staining is negative, using 1 or 2 additional antibodies from other companies that recognize different antigens may reveal the involved light chain. Amyloid can be “sticky” and may have weak to moderate staining for a nonpathogenic protein. Additionally, it is possible to have 2 different types of amyloid infiltrating 1 organ. If the implicated protein does not match the expected pattern (ie, ATTR staining of amyloid only in the renal medullary interstitium) or it is suspected there may be more than 1 type of amyloid present, mass spectrometry is indicated to definitively identify the amyloid type(s).

**CONCLUSIONS**

Amyloid deposits are a rare occurrence, although they are seen with more frequency in large subspecialized pathology practices. If the amyloid type is not determined, there may be substandard or incorrect care for patients. The IHC typing of amyloid can be achieved when performed in subspecialized departments with experience and relatively frequent use of IHC for this reason, or by reference laboratories. For accurate IHC typing, an appropriate panel of amyloid type–specific antibodies is needed for comparative evaluation. Therefore, using the proposed organ-based algorithms can be helpful in providing clinicians with a more specific differential diagnosis to help guide clinical evaluation and highlight the need for amyloid identification. Cases in which IHC is not available or the amyloid type cannot be determined with confidence should be typed via mass spectrometry for optimal patient care.

**References**


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