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the assembly of light and heavy chains because they appear to contain both in their cytoplasm. Such patients are not treated differently from other patients with CLL (Chap. 107). ■ ■FURTHER READING Corre J et al: Risk factors in multiple myeloma: is it time for a revision? Blood 137:16, 2021. Hideshima T, Anderson KC: Signaling pathway mediating myeloma cell growth and survival. Cancers (Basel) 13:216, 2021. Hillengass J et al: International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders. Lancet Oncol 20:e302, 2019. Kumar S et al: International Myeloma Working Group consensus crite ria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 17:e328, 2016. Moreau P et al: Treatment of relapsed and refractory multiple myeloma: Recommendations from the International Myeloma Work ing Group. Lancet Oncol 22:e105, 2021. Munshi NC et al: A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. Blood Adv 4:5988, 2020. Raje NS et al: Consensus guidelines and recommendations for infec tion prevention in multiple myeloma: A report from the International Myeloma Working Group. Lancet Haematol 9:e143 2022. Rajkumar SV et al: International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 15:e538, 2014. Richardson PG et al: Triplet therapy, transplantation, and mainte nance until progression in myeloma. N Engl J Med 387:132, 2022. Robiou du Pont S et al: Genomics of multiple myeloma. J Clin Oncol 35:963, 2017. Terpos E et al: Treatment of multiple myeloma-related bone disease: Recommendations from the Bone Working Group of the Interna tional Myeloma Working Group. Lancet Oncol 22:e119, 2021. Treon SP et al: How I use genomics and BTK inhibitors in the treat ment of Waldenstrom macroglobulinemia. Blood 143:1702, 2024. John L. Berk, Vaishali Sanchorawala

Amyloidosis ■ ■GENERAL PRINCIPLES Amyloidosis is the term for a group of protein misfolding disorders characterized by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. A robust cellular machinery exists to chaperone proteins during the process of synthesis and secretion, to ensure that they achieve correct tertiary conformation and function, and to eliminate proteins that misfold. However, genetic mutation, incorrect processing, and other factors may favor misfolding, with consequent loss of normal protein function and intracellular or extra cellular aggregation. Many diseases, ranging from cystic fibrosis to Alzheimer’s disease, are now known to involve protein misfolding. In the amyloidoses, the aggregates are typically extracellular, and the misfolded protein subunits assume a common antiparallel, β-pleated sheet–rich structural conformation that leads to the formation of higher-order oligomers and then fibrils with unique staining proper ties. The term amyloid was coined around 1854 by the pathologist Rudolf Virchow, who thought that these deposits resembled starch (Latin amylum) under the microscope. Amyloid diseases, defined by the biochemical nature of the protein composing the fibril deposits, are classified according to whether they are systemic or localized,

whether they are acquired or inherited, and their clinical patterns (Table 117-1). The standard nomenclature is

AX, where A indicates amyloidosis and X represents the protein pres ent in the fibril. This chapter focuses primarily on the systemic forms. AL amyloidosis refers to amyloid composed of immunoglobulin light chains; this disorder, formerly termed primary systemic amyloidosis, arises from a clonal B-cell or plasma cell disorder and can be associated with myeloma or lymphoma. ATTR amyloidosis, the most prevalent of the familial amyloidoses, refers to amyloid derived from wild-type or mutated transthyretin (TTR), the transport protein for thyroid hormone and retinol-binding protein. AA amyloid is composed of the acute-phase reactant protein serum amyloid A (SAA) and occurs in the setting of chronic inflammatory or infectious diseases; for this reason, this type was formerly known as secondary amyloidosis. Aβ2M amyloid results from misfolded β2-microglobulin, occurring in individuals with long-standing renal disease who have undergone dialysis, typically for years. Aβ, the most common form of localized amyloidosis, is found in the brain of patients with Alzheimer's disease after abnormal pro teolytic processing and aggregation of polypeptides derived from the amyloid precursor protein.

Diagnosis and treatment of the amyloidoses rest upon the histopath ologic identification of amyloid deposits and immunohistochemical, biochemical, or genetic determination of amyloid type (Fig. 117-1). In the systemic amyloidoses, the clinically involved organs can be biopsied, but amyloid deposits may be found in any tissue of the body. Historically, blood vessels of the gingiva or rectal mucosa were often examined, but the most easily accessible tissue—positive in more than 80% of patients with systemic amyloidosis—is abdominal fat. After local anesthesia, fat is aspirated with a 16-gauge needle from the subcu taneous layer of the abdominal wall. Fat globules expelled onto a glass slide can be stained for amyloid by Congo red dye, thus avoiding a sur gical procedure. If this material is negative, more invasive biopsies of the involved organ like kidney, heart, liver, tongue, or gastrointestinal tract can be considered in patients in whom amyloidosis is suspected. The regular β-sheet structure of amyloid deposits exhibits a unique "green" birefringence by polarized light microscopy when stained with Congo red dye; other regular protein structures (e.g., collagen) appear white under these conditions. The 10-nm-diameter fibrils can also be visualized by electron microscopy of paraformaldehyde-fixed tissue. Once amyloid is found, the precursor protein type must be determined by immunohistochemistry, immunoelectron microscopy, or extraction and biochemical analysis employing mass spectrometry; gene sequenc ing is used to identify mutants causing hereditary amyloidosis. How ever, a mass spectrometry–based analysis of the amyloid-containing tissues is now considered the best approach, with a reported sensitivity of 88% and specificity of 96%, which are higher than immunochemical techniques, and this technique does not require a large panel of antisera to identify non-AL amyloidosis. The patient's history, physical find ings, and clinical presentation, including age and ethnic origin, organ system involvement, underlying diseases, and family history, may pro vide helpful clues as to the type of amyloidosis. However, there can be considerable overlap in clinical presentations, and accurate typing of the amyloidogenic protein is essential to guide appropriate therapy and offer genetic counseling as appropriate. CHAPTER 117 Amyloidosis The mechanisms of fibril formation and tissue toxicity remain con troversial. The "amyloid hypothesis," as it is currently understood, pro poses that precursor proteins undergo a process of reversible unfolding or misfolding; misfolded proteins form oligomeric aggregates, higherorder polymers, and then fibrils that deposit in tissues. Accumulating evidence suggests that the oligomeric intermediates may constitute the most toxic species.

Oligomers are more capable than fibrils of interact ing with cells and inducing formation of reactive oxygen species and stress signaling. Ultimately, the fibrillar tissue deposits are likely to interfere with normal organ function. However, direct proteotoxicity of the soluble oligomers also can lead to organ dysfunction. A more sophisticated understanding of the mechanisms leading to amyloid formation and cell and tissue dysfunction will continue to provide new targets for therapies. The clinical syndromes of the amyloidoses are associated with rela tively nonspecific alterations in routine laboratory tests. Blood counts are usually normal, although the erythrocyte sedimentation rate is

TABLE 117-1 Amyloid Precursor Proteins and Their Clinical Syndromes DESIGNATION PRECURSOR CLINICAL SYNDROME CLINICAL INVOLVEMENT Systemic Amyloidoses AL Immunoglobulin light chain Primary or myeloma-associateda Any AH Immunoglobulin heavy chain Rare variant of primary or myeloma-associated Any AA Serum amyloid A protein Secondary; reactiveb Renal, heart, other Aβ2M β2-Microglobulin Hemodialysis-associated Synovial tissue, bone ATTR Transthyretin Familial (mutant) Age-related (wild type) AApoAI Apolipoprotein AI Familial Hepatic, renal AApoAII Apolipoprotein AII Familial Renal Agel Gelsolin Familial Cornea, cranial nerves, skin, renal AFib Fibrinogen Aa Familial Renal, vascular ALys Lysozyme Familial Renal, hepatic ALECT2 Leukocyte chemotactic factor 2 Undefined Renal Localized Amyloidoses Aβ Amyloid β protein Alzheimer’s disease; Down’s syndrome Central nervous system ACys Cystatin C Cerebral amyloid angiopathy Central nervous system, vascular APrP Prion protein Spongiform encephalopathies Central nervous system AIAPP Islet amyloid polypeptide (amylin) Diabetes-associated Pancreas PART 4 Oncology and Hematology Acal Calcitonin Medullary carcinoma of the thyroid Thyroid AANF Atrial natriuretic factor Atrial fibrillation Cardiac atria APro Prolactin Endocrinopathy Pituitary ASgl Semenogelin I Age-related; incidental autopsy or biopsy finding Seminal vesicles aLocalized AL deposits can occur in skin, conjunctiva, urinary bladder, and the tracheobronchial tree. bSecondary to chronic inflammation or infection or to a hereditary periodic fever syndrome such as familial Mediterranean fever. CLINICAL SUSPICION OF AMYLOIDOSIS Noninvasive Tissue Biopsy (Congo red staining of abdominal fat or other tissue) + – Invasive Tissue Biopsy (Congo red staining of affected major organs) + – No further work-up Identify Diagnosis Mass spectrometry or IHC of amyloid deposits Kappa or lambda light chain AL amyloidosis (Screen for cardiac, renal, hepatic, autonomic involvement, and factor X deficiency) Monoclonal protein in serum or urine Plasma cell dyscrasia in bone marrow Amyloid A protein Underlying chronic inflammatory disease AA amyloidosis (Screen for renal, hepatic involvement) Transthyretin Mutant transthyretin +/– family history ATTRm familial amyloidosis (Screen for neuropathy, cardiomyopathy; screen relatives) Wild-type transthyretin (usually males >65, cardiac) ATTRwt or age-related amyloidosis Negative Mutant ApoAI, ApoAII, fibrinogen, lysozyme, gelsolin Familial amyloidosis of rare type (Screen for renal, hepatic, GI involvement) FIGURE 117-1 Algorithm for the diagnosis of amyloidosis and determination of type. Clinical suspicion: unexplained nephropathy, cardiomyopathy, neuropathy, enteropathy, arthropathy, and macroglossia. ApoAI, apolipoprotein AI; ApoAII, apolipoprotein AII; GI, gastrointestinal; IHC, immunohistochemistry.

Cardiac, peripheral and autonomic nerves, soft tissues, spine, bladder frequently elevated. Patients with glomerular kidney involvement generally have proteinuria, often in the nephrotic range, leading to hypo albuminemia that may be severe; patients with serum albumin levels <2 g/dL generally have pedal edema or anasarca. Amyloid cardiomy opathy is characterized by concentric ventricular hypertrophy and diastolic dysfunction associated with elevation of brain natriuretic

peptide (BNP) or N-terminal pro–brain natriuretic peptide (NT-proBNP) as well as troponin. These car diac biomarkers can be used for disease staging, prognostication, and disease activity monitoring in patients with AL amyloidosis. Notably, renal insufficiency can falsely elevate levels of these bio markers. Biomarkers of cardiac remodeling—

that is, matrix metalloproteinases and tissue inhibitors of metalloproteinases—are altered in the serum of patients with amyloid cardiomy opathy. Electrocardiographic and echocardio graphic features of amyloid cardiomyopathy are described below. Patients with liver involvement, even when advanced, usually develop cholestasis with an elevated alkaline phosphatase concentra tion with minimal alteration of the aminotrans ferases and preservation of synthetic function. In AL amyloidosis, endocrine organs may be involved, and hypothyroidism, hypoadrenalism, or even hypopituitarism can occur. Although none of these findings is specific for amyloidosis, the presence of abnormalities in multiple organ systems should raise suspicions of the diagnosis. ■ ■AL AMYLOIDOSIS Etiology and Incidence AL amyloidosis is most frequently caused by a clonal expansion of

bone marrow plasma cells that secrete a monoclonal immunoglobulin light chains forming amyloid fibrils and deposits in tissues. Whether the clonal plasma cells produce a light chain that misfolds and leads to AL amyloidosis or a light chain that folds properly, allowing the cells to inexorably expand over time and develop into multiple myeloma (Chap. 116), may depend upon primary sequence of the clonal light chain or other genetic or epigenetic factors. AL amyloidosis can occur with multiple myeloma or other B lymphoproliferative diseases, includ ing non-Hodgkin’s lymphoma (Chap. 113) and Waldenström’s macro globulinemia (Chap. 116). AL amyloidosis is the most common type of systemic amyloidosis diagnosed in North America. Its incidence has been estimated at 8–12 cases per 100,000 population; however, ascer tainment continues to be inadequate, and the true incidence may be much higher. AL amyloidosis, like other plasma cell disorders, usually occurs after age 40 and is often progressive and fatal if untreated. Pathology and Clinical Features Amyloid deposits are usually widespread in AL amyloidosis and can be present in the interstitium of any organ outside the central nervous system. The amyloid fibril deposits are composed of full-length 23-kDa monoclonal immuno globulin light chains as well as fragments. Accessory molecules codeposited with light chain fibrils (as well as with other amyloid fibrils) include serum amyloid P component, apolipoproteins e and A-IV, glycosaminoglycans, and metal ions. Although all kappa and lambda light chain subtypes have been identified in AL amyloid fibrils, lambda subtypes predominate. AL amyloidosis is often a rapidly progressive disease that presents as a pleiotropic set of clinical syndromes, recognition of which is key for initiation of the appropriate workup. Nonspecific symptoms of fatigue and weight loss are common; however, the diagnosis is rarely considered until symptoms referable to a specific organ develop. The kidneys are a frequently involved organ and are affected in 60–70% of patients. Renal amyloidosis usually manifests as proteinuria, often in the nephrotic range and associated with hypoalbuminemia, second ary hypercholesterolemia and hypertriglyceridemia, and edema or anasarca. In some patients, interstitial rather than glomerular amyloid deposition can produce azotemia without proteinuria. The heart is the other commonly affected organ (70–80% of patients), and cardiac involvement is the leading cause of death from AL amyloidosis. Early on, the electrocardiogram may show low voltage in the limb leads with a pseudo-infarct pattern. Echocardiographic features of disease include concentrically thickened ventricles and diastolic dysfunction with an abnormal global longitudinal strain pattern; a “sparkly” appearance has been described but is often not seen

with modern high-resolution echocardiographic techniques. Poor atrial contractility occurs even in sinus rhythm, and patients with cardiac amyloidosis are at risk for development of atrial thrombi and thromboembolic complications. Cardiac magnetic resonance imaging (MRI) can show increased wall thickness and characteristic delayed gadolinium enhancement of the subendocardium. Nervous system symptoms include peripheral sen sorimotor neuropathy and/or autonomic dysfunction manifesting as gastrointestinal motility disturbances (early satiety, diarrhea, constipa tion), dry eyes and mouth, impotence, orthostatic hypotension, and/ or neurogenic bladder. Macroglossia (Fig. 117-2A), a pathognomonic sign of AL amyloidosis, is seen in only ~10% of patients. Liver involve ment causes cholestasis and hepatomegaly. The spleen is frequently involved, and there may be functional hyposplenism in the absence of significant splenomegaly. Many patients experience “easy bruising” due to amyloid deposits in capillaries or deficiency of clotting factor X due to binding to amyloid fibrils; cutaneous ecchymoses appear, particularly around the eyes, producing another uncommon but pathognomonic finding, the “raccoon-eye” sign (Fig. 117-2B). Other findings include nail dystrophy (Fig. 117-2C), alopecia, and amyloid arthropathy with thickening of synovial membranes in the wrists and shoulders. The presence of a multisystemic illness or general fatigue along with any of these clinical syndromes should prompt a workup for amyloidosis. Diagnosis Identification of an underlying clonal plasma cell or B lymphoproliferative process and a clonal light chain are key to the

A CHAPTER 117 B Amyloidosis C FIGURE 117-2 Clinical signs of AL amyloidosis. A. Macroglossia. B. Periorbital ecchymoses. C. Fingernail dystrophy. diagnosis of AL amyloidosis. Serum protein electrophoresis and urine protein electrophoresis, although of value in multiple myeloma, are not useful screening tests if AL amyloidosis is suspected because the clonal light chain or whole immunoglobulin often is not present in sufficient amounts to produce a monoclonal “M-spike” in the serum or light chain (Bence Jones) protein in the urine. However, more than 90% of patients with AL amyloidosis have serum or urine monoclonal light chain or whole immunoglobulin detectable by immunofixation electrophoresis of serum (SIFE) or urine (UIFE) (Fig. 117-3A) or by nephelometric measurement of serum “free” light chains (i.e., light chains circulating in monomeric form rather than in an immuno globulin tetramer with heavy chain). Examining the ratio as well as the absolute amount of serum-free light chains is essential, as renal insuf ficiency reduces light chain clearance, nonspecifically elevating both isotypes. In addition, an increased percentage of plasma cells in the bone marrow—typically 5–30% of nucleated cells—is found in ~90% of patients. Kappa or lambda clonality should be demonstrated by flow cytometry, immunohistochemistry, or in situ hybridization for light chain mRNA (Fig. 117-3B). More sensitive mass spectrometry–based assays can have higher levels of detection for low concentration of monoclonal protein. A monoclonal serum protein by itself is not diagnostic of amy loidosis, since monoclonal gammopathy of uncertain significance is common in older patients (Chap. 116). However, when monoclonal gammopathy of uncertain significance is found in patients with biopsyproven amyloidosis, the AL type should be ruled out. Similarly, patients thought to have “smoldering myeloma” because of a modest elevation of bone-marrow plasma cells should be screened for AL amyloidosis if

A PART 4 Oncology and Hematology B FIGURE 117-3 Laboratory features of AL amyloidosis. A. Serum immunofixation electrophoresis reveals an IgGκ monoclonal protein in this example; serum protein electrophoresis is often normal. B. Bone marrow biopsy sections stained by immunohistochemistry with antibody to CD138 (syndecan, highly expressed on plasma cells) (left) or by in situ hybridization with fluorescein-tagged probes (Ventana Medical Systems) binding to κ

mRNA (center) and λ mRNA (right) in plasma cells. (Photomicrograph courtesy of C. O'Hara; with permission.) they have signs or symptoms of renal, cardiac, or neurologic disease. Accurate tissue amyloid typing is essential for appropriate treatment. Immunohistochemical staining of the amyloid deposits is useful if they selectively bind one light chain antibody in preference to the other; some AL deposits bind antibodies nonspecifically. Commercial antibodies used for immunohistochemistry may not be accurate in amyloid typing. Immunoelectron microscopy is more reliable; laser capture microdissection and tandem mass spectrometry–based typing of the amyloid precursor protein have become the diagnostic standard. In ambiguous cases, other forms of amyloidosis should be thoroughly excluded with appropriate genetic and other testing. Staging System and Risk Stratification The current staging systems for systemic AL amyloidosis are based on the biomarkers of plasma cell dyscrasia and cardiac and renal involvement. The Mayo 2004 staging system is based on the levels of NT-proBNP and cardiac troponins and was modified by European investigators to identify and classify very-high-risk patients. This cardiac staging system is the most widely used to determine patient management. This staging system was modified (Mayo 2012) to include clonal burden, assessed by dFLC (difference between involved and uninvolved circulating free light chain) concentration, which has independent ability to predict survival. Boston University investigators introduced a staging system incorporating BNP and troponin I that also is able to predict survival.

Patients with AL amyloidosis with a very low (<50 mg/L) dFLC level have a significantly better outcome irrespective of cardiac stage. A renal staging system based on 24-h urine protein excretion and esti mated glomerular filtration rate (eGFR) predicting the progression to dialysis at 2 years has also been developed and validated. Several other biomarkers have been shown to predict outcomes and survival but have not been incorporated in staging systems yet. TREATMENT AL Amyloidosis Extensive multisystemic involvement typifies AL amyloidosis, and historically, the median survival without treatment was usually only ~1–2 years from the time of diagnosis. Marked progress in the outcome and survival has taken place over the past four decades with advent of new therapies, increased awareness, and accurate diagnosis. Current therapies target the clonal bone marrow plasma cells, using approaches employed for multiple myeloma. High-dose intravenous (IV) melphalan followed by autologous stem cell trans plantation (HDM/SCT) produces complete hematologic responses in ~40% of treated patients, as determined by loss of clonal plasma cells in the bone marrow and disappearance of the amyloidogenic monoclonal light chain, as determined by SIFE/UIFE and free light chain quantitation. Six to 12 months after achieving a hematologic response, improvements in organ function and quality of life may occur. Hematologic responses appear to be more durable after HDM/SCT than in multiple myeloma, with remissions continuing in some patients beyond 15 years without additional treatment. Unfortunately, only ~20–30% of all AL amyloidosis patients are suitable for aggressive treatment, and even at specialized treat ment centers, transplantation-related morbidity and mortality rates are higher than those for other hematologic diseases because of impaired organ function at initial presentation. Amyloid cardiomy opathy, poor nutritional and performance status, and multiorgan disease contribute to excess morbidity and mortality. A bleeding diathesis resulting from adsorption of clotting factor X to amy loid fibrils also increases mortality rates; however, this syndrome occurs in only 5–10% of patients. A randomized multicenter trial conducted in France compared oral melphalan and dexamethasone with HDM/SCT and failed to show a benefit of dose-intensive treat ment, although the transplantation-related mortality rate in this study was very high. It has become clear that careful selection of patients and expert peritransplantation

management are essential in reducing transplantation-related complications. The best therapy for those who are not eligible to receive SCT is based on a U.S. Food and Drug Administration–approved therapy of CyBorD (cyclophosphamide, bortezomib [a protea some inhibitor], and dexamethasone) with daratumumab. Patient characteristics should be considered when choosing a regimen; for example, treatment with bortezomib plus oral melphalan and dexa methasone (MDex) can overcome the effects of both gain of 1q21 (which confers a poorer outcome with oral melphalan) and t(11;14) (which confers a poorer outcome with bortezomib). Transplantineligible patients in whom bortezomib is contraindicated due to preexisting peripheral neuropathy can be treated with MDex or combinations based on immunomodulatory drugs (e.g., lenalido mide or pomalidomide). High-risk patients represent ~15–20% of all individuals with AL amyloidosis and are a challenge owing to advanced cardiac stage (IIIb) or severe heart failure (New York Heart Association class III or IV) as they are excluded from most of the clinical trials. Novel antifibril monoclonal antibodies are currently undergoing clinical trials in combination with treatments directed against the plasma cell dyscrasia (CyBorD plus daratumumab [anti-CD38]) in patients with newly diagnosed AL amyloidosis. Clinical trials are essential in improving therapy for this rare disease. Supportive care is important for patients with any type of amy loidosis. For nephrotic syndrome, diuretics and support stockings

can ameliorate edema; angiotensin-converting enzyme inhibitors should be used with caution and have not been shown to slow renal disease progression. Effective diuresis can be facilitated with albumin infusions to raise intravascular oncotic pressure. Conges tive heart failure due to amyloid cardiomyopathy is best treated with diuretics; it is important to note that digitalis, calcium channel blockers, and beta blockers are relatively contraindicated as they can interact with amyloid fibrils and produce heart block and wors ening heart failure. Amiodarone has been used for atrial and ven tricular arrhythmias. Automatic implantable defibrillators appear to have reduced effectiveness due to the thickened myocardium, but they may benefit some patients. Atrial ablation is an effective approach for atrial fibrillation. For conduction abnormalities, ven tricular pacing may be indicated. Atrial contractile dysfunction is common in amyloid cardiomyopathy and associated with increased thromboembolic complications, prompting considerations of anti coagulation even in the absence of atrial fibrillation. Autonomic neuropathy can be treated with α agonists such as midodrine to support postural blood pressure; gastrointestinal dysfunction may respond to motility or bulk agents. Nutritional supplementation, either oral or parenteral, is also important. In localized AL amyloidosis, amyloid deposits can be produced by clonal plasma cells infiltrating local sites in the airways, bladder, skin, or lymph nodes (Table 117-1). These deposits may respond to surgical intervention or elimination of the responsible plasma cell clone by low-dose radiation therapy (typically only 20 Gy); systemic treatment generally is not appropriate. Patients should be referred to a center familiar with management of these rare manifestations of amyloidosis. ■ ■AA AMYLOIDOSIS Etiology and Incidence AA amyloidosis can occur in association with almost any chronic inflammatory state (e.g., rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, familial Medi terranean fever [Chap. 381], or other periodic fever syndromes) or chronic infections such as tuberculosis, osteomyelitis, or subacute bac terial endocarditis. In the United States and Europe, AA amyloidosis has become less common, occurring in fewer than 2% of patients with these diseases, presumably because of advances in anti-inflammatory and antimicrobial therapies. It has also been described in associa tion with Castleman’s disease, lymphomas, and renal cell carcinoma, emphasizing the diagnostic importance of computed tomography (CT) scanning to look for such tumors as well as serologic and microbiologic studies. In

up to 20% of patients, AA amyloidosis can also be seen with out any identifiable underlying disease. Pathology and Clinical Features Organ involvement in AA amyloidosis usually begins in the kidneys. Hepatomegaly, splenomeg aly, and autonomic neuropathy can also occur as the disease progresses; cardiomyopathy is a late manifestation in ~10–25% of patients. The symptoms and signs of AA disease cannot be reliably distinguished from those of AL amyloidosis. AA amyloid fibrils are usually composed of an 8-kDa, 76-amino-acid N-terminal portion of the 12-kDa precur sor protein SAA. This acute-phase protein is synthesized in the liver and transported by high-density lipoprotein (HDL3) in the plasma. Several years of an underlying inflammatory disease causing chronic elevation of SAA levels usually precede fibril formation, although infections can lead to AA amyloid deposition more rapidly. TREATMENT AA Amyloidosis Primary therapy for AA amyloidosis consists of treatment of the underlying inflammatory or infectious disease. Treatment that sup presses or eliminates the inflammatory state or infection decreases the circulating levels of SAA, slowing the rate of amyloid fibril formation. For familial Mediterranean fever, colchicine at a dose of 1.2–1.8 mg/d is the standard treatment. However, colchicine has

not been helpful for AA amyloidosis of other causes or for other amyloidoses. Tumor necrosis factor and interleukin 1 and inter leukin 6 antagonists can effectively interrupt cytokine signaling that drives many inflammatory syndromes, inhibiting hepatic SAA production and limiting AA amyloid deposition. Development of a fibril-specific agent (eprodisate) that interferes with the interaction of serum amyloid A protein and glycosaminoglycans to prevent or disrupt fibril formation failed in phase 3 trials.

■ ■ATTR AND OTHER HEREDITARY AMYLOIDOSES The familial amyloidoses are autosomal dominant diseases in which mutated or variant plasma proteins misfold or aggregate to form betasheet rich amyloid deposits. These diseases are rare, with an estimated case incidence of <1/100,000 population in the United States, although founder effects in remote areas of Portugal, Sweden, and Japan pro duce a higher local prevalence of disease. The most prevalent form of hereditary amyloidosis arises from mutation of the abundant liverderived plasma protein transthyretin (TTR, also known as prealbumin) and is termed ATTR variant (ATTRv) amyloid. More than 130 TTR mutations typically conferring one-amino-acid substitutions have been described, with most inducing clinical ATTR amyloid disease. Toxic TTR oligomers and ATTR amyloid deposits target peripheral and auto nomic nervous systems and the heart. One TTR variant, V122I, occurs in nearly 4% of the African-American and Afro-Caribbean populations and is associated with late-onset cardiac amyloidosis. The actual inci dence and penetrance of disease in the African-American population are the subject of ongoing research, but consideration of V122I ATTR amyloidosis is warranted in African-American patients who present with concentric cardiac hypertrophy and evidence of diastolic heart failure, particularly in the absence of a history of hypertension or valvular disease. Other familial amyloidoses, caused by variant apoli poproteins AI or AII, gelsolin, fibrinogen Aα, or lysozyme, are reported with lower prevalence worldwide. New amyloidogenic serum proteins continue to be identified periodically, including leukocyte chemotactic factor LECT2, which is a cause of renal amyloidosis in Hispanic and Pakistani populations. Although the clustering of ALECT2 cases sug gests heritability, no LECT2 gene-coding sequence variations have been identified. CHAPTER 117 Amyloidosis Normal (wild-type) transthyretin can also misfold and aggregate to form ATTR amyloid, principally expressed in men beginning in the seventh decade with increasing prevalence with age. Formerly termed senile systemic amyloidosis, ATTRwt amyloid is reported at autopsy in 25% of hearts from male patients who are 80 years and older. Although it

is unclear why a wild-type protein becomes amyloidogenic, aging inefficiencies of intracellular quality-assurance mechanisms (termed the unfolded protein response) likely predispose to secretion of pro teins prone to misaggregation. Due to the numbers of aging men globally, ATTRwt is the most prevalent and rapidly growing form of amyloidosis in the world today. Data to date characterize ATTRwt amyloidosis as a disease of aging, not inheritance. Clinical Features and Diagnosis ATTRv amyloidosis has varied presentations predicted by the specific TTR mutation. Consequently, kindreds typically express similar disease timing and clinical course. Apparent sporadic presentations (no recognized family history) often reflect incomplete penetrance of the TTR mutation and not a sponta neous event. ATTRv amyloidosis presents as familial amyloidotic poly neuropathy (nerve damage) or familial amyloidotic cardiomyopathy (heart damage), although the majority of cases exhibit multiorgan dis ease. Peripheral neuropathy begins as a length-dependent small-fiber sensorimotor neuropathy first exhibited in the feet with ascending progression to the upper extremities. Autonomic neuropathy manifests as smooth muscle dysmotility (dysphagia, diarrhea, urinary retention), vascular dysregulation (orthostatic hypotension, erectile dysfunction), and anhidrosis. Soft tissue disease (carpal tunnel syndrome, tendi nopathy, and spinal stenosis) commonly precedes nerve or heart mani festations of disease by one to two decades, particularly in ATTRwt amyloid patients who frequently report bicipital, patellar, or Achilles tendon rupture. Less common expressions of ATTRv include vitreous

opacities and leptomeningeal amyloid deposition from variant protein produced by the retinal epithelium and choroid plexus, respectively. ATTR amyloid involvement of the heart is clinically better tolerated than AL amyloid cardiomyopathy as reflected by both the time from heart failure presentation to death in untreated cases of ATTR (median 42–48 months) versus AL (median 6 months) amyloidosis, and the dramatically greater burden of disease by echocardiographic measures at symptomatic presentation.

Typical syndromes associated with non-ATTR forms of hereditary (AF) disease include renal amyloidosis with mutant fibrinogen, lyso zyme, or apolipoproteins; hepatic amyloidosis with apolipoprotein AI; and amyloidosis of cranial neuropathy with corneal lattice dystrophy pathognomonic of gelsolin (Finnish) amyloidosis. Patients with AF amyloidosis can present with clinical syndromes that mimic those of patients with AL disease. Rarely, AF carriers can develop AL disease or AF patients may have monoclonal gammopathy without AL. Thus, it is important to screen for plasma cell disorders and for protein muta tions in patients with amyloidosis. Although mass spectrometry often detects amino acid sequence variations, it is not designed to definitively identify specific protein variations; DNA sequencing is the diagnostic standard for AF mutations. TREATMENT ATTR Amyloidosis PART 4 Oncology and Hematology Untreated, survival after onset of ATTR disease is 4–15 years depending on whether the disease affects primarily the heart or nervous system, respectively. To date, therapeutic strategies used to control ATTR amyloidosis include: (1) orthotopic liver trans plantation (OLT) to replace the factory of the mutated protein (only applicable to ATTRv); (2) stabilization of circulating TTR tetramers, preventing TTR monomer release and amyloid fibril formation; and (3) TTR gene silencing (RNA interference or anti sense oligonucleotide agents), suppressing hepatic TTR production and subsequent ATTR fibril formation. After nearly 30 years as the principal treatment, OLT is now rarely employed, limited to patients with ATTRv amyloid, early peripheral neuropathy (V30M ATTR), and minimal systemic amyloid burden. Patients with more extensive amyloid (late V30M and non-V30M TTR mutations) who undergo OLT often suffer posttransplant disease progression due to allograft wild-type ATTR

complexing on preexisting amy loid deposits. The TTR small-molecule thyroxine mimetic agents, diflunisal and tafamidis, bind to the kinetically stable tetrameric TTR conformation, limiting release and misfolding of monomeric protein, which is the critical step in TTR amyloidogenesis. Inter national phase 3 randomized controlled trials demonstrate that TTR stabilizers slow but infrequently stop progression of ATTR polyneuropathy (diflunisal) and cardiomyopathy (tafamidis). TTR gene silencers (patisiran, inotersen, vutrisiran, eplontersen) more reliably halt neurologic disease progression by minimizing produc tion of the amyloidogenic protein by the liver. Indeed, 35–60% of treated patients with familial amyloid polyneuropathy exhibit improved sensory nerve deficits, a novel finding. Therapeutic drug trials are underway to examine the safety, tolerability, and effective ness of TTR gene silencers for ATTR cardiomyopathy. Preliminary data suggest TTR gene silencers may promote heart remodeling and improve systolic function in patients with wild type and variant ATTR amyloid cardiomyopathy. Future clinical trials are set to examine the applicability of (1) one-time CRISPR/cas9 gene editing or (2) ATTR amyloid-depleting antibodies in patients with either ATTR polyneuropathy or cardio myopathy. These antibodies are designed to recognize and bind nonnative (misfolded) TTR epitopes, mobilizing macrophages and monocytes to disrupt existing amyloid deposits. Whether disrupt ing amyloid deposits renews heart and nerve function will be deter mined by the outcome of these pivotal trials. The extraordinary pace of drug development harnessing cuttingedge science in this orphan disease has extended survival and

improved quality of life. Ironically, these advances expose pre viously unrecognized leptomeningeal (brain) and vitreous (eye) ATTR disease due to their occurrence late in disease, highlighting the unmet need for effective amyloid treatments that penetrate the blood-brain barrier. ■ ■Aa2M AMYLOIDOSIS Aβ2M amyloid is composed of β2-microglobulin, the invariant chain of class I human leukocyte antigens, and produces rheumatologic manifestations in patients undergoing long-term hemodialysis and, rarely, in patients with a hereditary form of disease. β2-Microglobulin is excreted by the kidney, and levels become elevated in end-stage renal disease. The molecular mass of β2M is 11.8 kDa—above the cutoff of some dialysis membranes. The incidence of this disease appears to be declining with the use of newer membranes in high-flow dialysis tech niques. Aβ2M amyloidosis usually presents as carpal tunnel syndrome, persistent joint effusions, spondyloarthropathy, or cystic bone lesions. Carpal tunnel syndrome is often the first symptom. In the past, persis tent joint effusions accompanied by mild discomfort were found in up to 50% of patients who had undergone dialysis for >12 years. Involve ment is bilateral, and large joints (shoulders, knees, wrists, and hips) are most frequently affected. The synovial fluid is noninflammatory, and β2M amyloid can be found if the sediment is stained with Congo red. Although less common, visceral β2M amyloid deposits do occa sionally occur in the gastrointestinal tract, heart, tendons, and subcu taneous tissues of the buttocks. There are no proven specific therapies for Aβ2M amyloidosis, but cessation of dialysis after renal allografting may lead to symptomatic improvement. SUMMARY A diagnosis of amyloidosis should be considered in patients with unexplained nephropathy, cardiomyopathy (particularly with diastolic dysfunction), neuropathy (either peripheral or autonomic), enter opathy, or the pathognomonic soft tissue findings of macroglossia or periorbital ecchymoses. Pathologic identification of amyloid fibrils can be made with Congo red staining of aspirated abdominal fat or of an involved-organ biopsy specimen. Accurate typing by a combination of immunologic, biochemical, and genetic testing is essential in select ing appropriate therapy (Fig. 117-1). Systemic amyloidosis should be considered a treatable condition, as anti–plasma cell chemotherapy is highly effective in AL disease and targeted therapies are being developed for AA and ATTR disease. The combination of precursor and end-organ amyloid therapeutics potentially provides not only dis ease control but also functional

and quality-of-life improvements for patients with amyloidosis. Tertiary referral centers can provide special ized diagnostic techniques and access to clinical trials for patients with these rare diseases. ■ ■FURTHER READING Adams D et al: Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: A randomized clinical trial. Amyloid 30:1, 2023. Coelho T et al: Eplontersen for hereditary transthyretin amyloidosis with polyneuropathy. JAMA 330:1448, 2023. Griffin JM et al: ATTR amyloidosis: Current and emerging man agement strategies: JACC: CardioOncology state-of-the-art review. JACC CardioOncol 3:488, 2021. Gustine JN et al: Predictors of hematologic response and survival with stem cell transplantation in AL amyloidosis: A 25-year longitudinal study. Am J Hematol 97:1189, 2022. Kastritis E et al: Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. N Engl J Med 385:46, 2021. Maurer MS et al: Patisiran treatment in patients with transthyretin cardiac amyloidosis. N Engl J Med 389:1553, 2023. Merlini G et al: Systemic immunoglobulin light chain amyloidosis. Nat Rev Dis Primers 4:38, 2018. Staron A et al: Marked progress in AL amyloidosis survival: A 40-year longitudinal natural history study. Blood Cancer J 11:139, 2021.

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