BLOOD RESEARCH
VOLUME 57 · NUMBER 2
June 2022
REVIEW ARTICLE

Multidisciplinary supportive care in systemic light chain amyloidosis

Bou Zerdan Maroun[1], Sabine Allam[2], Chakra P. Chaulagain[1]

[1]*Department of Hematology-Oncology, Myeloma and Amyloidosis Program, Maroone Cancer Center, Cleveland Clinic Florida, Weston, FL, USA,* [2]*Department of Medicine, Faculty of Medicine, University of Balamand, Beirut, Lebanon*

p-ISSN 2287-979X / e-ISSN 2288-0011
https://doi.org/10.5045/br.2022.2021227
Blood Res 2022;57:106-116.

Received on December 29, 2021
Revised on April 30, 2022
Accepted on May 4, 2022

Correspondence to
Chakra P. Chaulagain, M.D., FACP
Department of Hematology-Oncology, Myeloma and Amyloidosis Program, Maroone Cancer Center, Cleveland Clinic Florida, 2950 Cleveland Clinic Blvd, Weston, FL 33331, USA
E-mail: CHAULAC@ccf.org

Abstract

The immunoglobulin light-chain amyloidosis is a multisystemic disease which manifests by damage to the vital organs by light chain-derived amyloid fibril. Traditionally, the treatment has been directed to the underlying plasma cell clone with or without high dose chemotherapy followed by autologous stem cell transplantation using melphalan based conditioning. Now with the approval of highly tolerable anti-CD38 monoclonal antibody daratumumab based anti-plasma cell therapy in 2021, high rates of hematologic complete responses are possible even in patients who are otherwise deemed not a candidate for autologous stem cell transplantation. However, despite the progress, there remains a limitation in the strategies to improve symptoms particularly in patients with advanced cardiac involvement, those with nephrotic syndrome and autonomic dysfunction due to underlying systemic AL amyloidosis. The symptoms can be an ordeal for the patients and their caregivers and effective strategies are urgently needed to address them. The supportive care is aimed to counteract the symptoms of the disease and the effects of the treatment on involved organs' function and preserve patients' quality of life. Here we discuss multidisciplinary approach in a system-based fashion to address the symptom management in this dreadful disease. In addition to achieving excellent anti-plasma cell disease control, using treatment directed to remove amyloid from the vital organs can theoretically hasten recovery of the involved organs thereby improving symptoms at a faster pace. Ongoing phase III clinical trials of CAEL-101 and Birtamimab will address this question.

Key Words Supportive care, Multidisciplinary approach, Hematology, Amyloidosis, Light chain

INTRODUCTION

Systemic Immunoglobulin light chain (AL) amyloidosis is a complex and life-threatening disorder characterized by the formation of β pleated sheets from intact or fragmented monoclonal immunoglobulin light chains [1-4]. These amorphous insoluble deposits in the organs are often derived from the immunoglobulin light chains produced in the bone marrow by clonal plasma cell neoplasms (monoclonal gammopathy of undetermined significance-MGUS, smoldering multiple myeloma-SMM or multiple myeloma-MM). Less frequently, the light chain produced by various other non-plasma cell hematological malignancies such as Waldenstrom's macroglobulinemia (lymphoplasmacytic lymphoma), and non-lymphoplasmacytic lymphoma such as Chronic Lymphocytic Leukemia (CLL) and marginal zone lymphoma (MZL) can also form AL amyloid deposits in organs [3]. The Congo-philic amyloid deposits (Fig. 1) in AL can either remain confined within one organ and cause localized AL amyloidosis (e.g., localized pulmonary AL or laryngopharyngeal AL, skin limited AL or localized AL in a part of the gastrointestinal system) or AL deposition can occur in various tissues in vital organs throughout the body disrupting multiple organ functions causing systemic AL amyloidosis [1, 3, 4]. Of interest, amyloid deposits were found to have a predilection for certain organs such as the heart, kidney, peripheral nerves gastrointestinal system, bone marrow cavity and the liver. These deposits are resistant to degradation and can also cause direct toxicity to tissues and organ dysfunction by inducing a cascade of oxidative stress which leads to cell death [1]. The prognosis of AL localized to one site is excellent and there may not be an underlying systemic proliferative clonal plasma cell neoplasm or lymphoproliferative disorder.

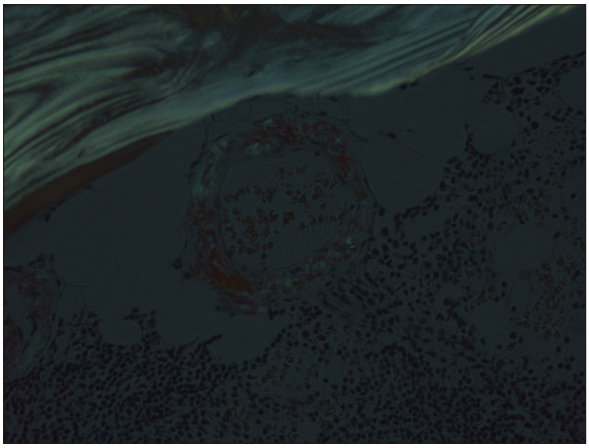

Fig. 1. Perivascular amyloid deposits demonstrated as apple green birefringence under polarized light in this Congo Red stain specimen from a patient with systemic AL amyloidosis due to lymphoplasmacytic lymphoma (Bone marrow Congo Red, ×20).

However, the prognosis of systemic AL amyloidosis with multiple organ involvement particularly with heart involvement is poor and there is almost always an identifiable clonal plasma cell neoplasm or lymphoproliferative disorder responsible for producing the amyloidogenic light chain as the precursor of the AL amyloidosis. Targeting the underlying clonal hematologic malignancy by chemotherapy or immunochemotherapy is the essential component of therapy in systemic AL amyloidosis to curb the production of amyloid precursor monoclonal light chain. In contrast, systemic chemoimmunotherapy is rarely used in localized AL amyloidosis. Around 4,000 new cases of AL amyloidosis are diagnosed each year in the US; therefore, it is classified as a rare disorder. Moreover, several studies have shown that AL amyloidosis tends to present in older adults with a median age of 64 at the time of diagnosis. Diagnosis is usually established late in the disease course, usually more than 1 year after symptom onset, due to the non-specific nature of the presentation and lack of adequate familiarity of the clinicians about this disease [1]. The diagnosis is often made late, and the patients are already too sick to tolerate systemic chemoimmunotherapy and the physicians are left with limited treatment options to prolong the survival of patients with AL systemic amyloidosis.

Historically, treatment has been limited to strategies that attempt to decrease the amount of amyloid precursor immunoglobulin light chain proteins produced in the bone marrow by targeting clonal bone marrow plasma cell disorder. This led to the use of proteasome inhibitors (e.g., bortezomib, carfilzomib), immunomodulatory agents (e.g., lenalidomide, pomalidomide) and autologous hematopoietic stem cell transplant (HSCT) after high dose melphalan (MEL) conditioning. The aim of these interventions is to suppress the progression of the organ dysfunction by halting the continuous production of clonal free light chains thereby preventing further deposition of amyloid deposits in vital organs [5]. However, one of the major limitations of this treatment strategy is that it has no effect on misfolded amyloid proteins already deposited in tissues of vital organs such as heart, kidneys and liver, which are the major cause of morbidity and mortality even after attainment of complete hematologic response [4]. Therefore, several researchers have highlighted the importance of targeting the organ dysfunction itself using fibril-directed therapies and supportive measures with the goal of cleaning or leaching out pre-formed amyloid deposits in the organs thereby restoring organ functions [6, 7]. One example of this strategy is the use of novel monoclonal antibody CAEL-101 in a phase II clinical trial (NCT04304144) given in combination with bortezomib, cyclophosphamide, and dexamethasone (CyBorD) [8] (NCT04512235 and *NCT04504825* respectively). Similarly, a Study to Evaluate the Efficacy and Safety of Birtamimab in Mayo Stage IV Patients with AL Amyloidosis (AFFIRM-AL) is currently ongoing NCT04973137 [9]. Targeting the plasma cell clone by anti-CD38-monoclonal antibody (MAB) such as daratumumab or isatuximab and the amyloid deposits by fibril directed MABs such as CAEL-101 and birtamimab (NEOD001) brings a novel concept of attacking the plasma cell clone (the cause of AL) and repairing the damaging effects of AL amyloid deposits in the vital organs.

In this review, we discuss updates in the diagnosis and staging of amyloidosis as well as the various symptomatic and supportive measures that can be employed to support the anti-plasma cell therapy and help ameliorate the organs dysfunction caused by systemic AL amyloidosis. Table 1 contains the major clinical problems and suggested supportive care in systemic AL Amyloidosis.

CARDIAC INVOLVEMENT IN AL AMYLOIDOSIS

Clinical picture

More than 50% of patients with AL amyloidosis are found to have cardiac involvement [10]. In general, cardiac amyloidosis involves the expansion of the extracellular space of the myocardial tissues which later contributes to chamber stiffening and thickening without compensatory dilation [11, 12]. The aforementioned cardiac wall stiffening and thickening manifests clinically as infiltrative and restrictive cardiomyopathy and diastolic dysfunction which progresses to heart failure with usually preserved left ventricular ejection fraction [1]. Early on, both radial and circumferential shortening of the myocardium are unaffected. Even in advanced stages, this pseudo-preservation gives a false impression that the ejection fraction is preserved. Consequently, patients commonly present with dyspnea on exertion, orthopnea, peripheral edema, and ascites. This later progresses to postural hypotension and even postural syncope at extreme cases. Moreover, arrhythmias, mainly atrial arrhythmias (atrial fibrillation or flutter), may be the initial presentation of patients with cardiac amyloidosis. This further contributes to the atrial dysfunction, which is commonly associated with an increased risk of thromboembolism leading to an elevated

Table 1. Major clinical problems and suggested supportive care in systemic AL amyloidosis.

Clinical syndrome	Intervention
Anasarca due to heart failure and/or nephrotic syndrome	Salt restriction and diuretics are the mainstay of treatment, tracking daily weight, collaboration and co-management with cardio-oncology and nephron-oncology when available
Ventricular or supra-ventricular tachy-arrhythmia	Amiodarone is the mainstay of treatment, collaboration with cardiac electrophysiology for trans-catheter ablation and need for anticoagulation to prevent thrombo-embolic complications
Sick sinus syndrome and heart blocks	Pacemakers, AICD remains controversial
Nephrotic syndrome	In addition to fluid management, clinicians should pay attention to the risk of accelerated atherosclerosis due to hyperlipidemia, risk of VTE and infections
Hypotension	Elastic stockings, postural training (avoiding sudden change in positions), judicious use of midodrine in severe cases, use of fludrocortisoneif limited cardiac or renal involvement
Peripheral neuropathy	Gabapentin, pregabalin are mainstay of therapy, SSRI can be useful, amitriptyline and nortriptyline should be avoided due to anti-cholinergic side effects
Malnutrition	Adequate calorie and protein intake is important, all patients should have a nutritional plan
Constipation	Metoclopramide can improve motility, stool softener both useful, osmotic laxatives e.g., milk of magnesium need to be avoided
Diarrhea	Loperamide may be useful,
Organ transplantation	1. Kidney transplantation for persistent ESRD or heart transplantation for refractory heart failure despite hematologic complete response 2. For young and otherwise fit patient with isolated severe cardiac involvement, heart transplant followed by chemotherapy or HSCT can be considered
Mental health	Anxiety and depression are common, routine screening with help of social worker or clinical psychologist is recommended.

Abbreviations: AICD, automatic implantable cardioverter defibrillator; ESRD, end stage renal disease; HSCT, autologous hematopoietic stem cell transplantation.

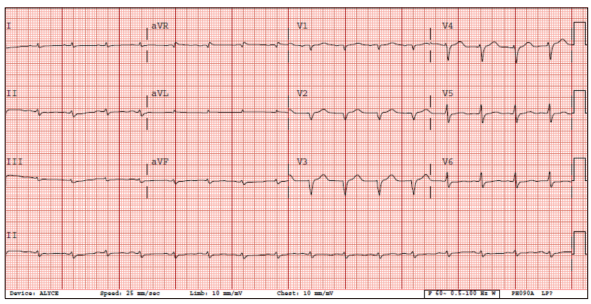

Fig. 2. An electrocardiogram (EKG) showing pseudo-infarction pattern or Q-waves in chest Leads V1-V3 in this 62-year-old man presenting with AL cardiomyopathy from underlying clonal plasma cell neoplasms. Both limb and chest lead also demonstrate presence of low voltage.

risk for ischemic stroke or peripheral arterial embolization leading to tissue ischemia or limb ischemia [11]. In most cases, cardiac AL amyloidosis' initial presentation can be sudden and rapidly progressive. Low voltage electrocardiogram (EKG) patterns, pseudo-infarct patterns, or conduction abnormalities are frequently found on EKG (Fig. 2).

In AL amyloidosis, the significance of early diagnosis of cardiac amyloidosis cannot be emphasized enough [11]. If left untreated, the median survival from the onset of heart failure symptoms is found to be only about 6 months in advanced cases [11]. Therefore, the various diagnostic modalities utilized focusing on early diagnosis have been of extensive interest among researchers.

Frequently, no single pathognomonic sign or symptom of cardiac amyloidosis can be found on physical exam. However, in some instances, careful inspection of the patient might reveal an elevated jugular venous pressure or distended neck veins. Moreover, the presence of hepatomegaly, peripheral edema and ascites indicative of right sided heart failure might be found in advanced cases. As a result, physicians are frequently directed towards laboratory tests and non-invasive imaging modalities [12]. The laboratory tests used aim to detect paraproteinemia include serum protein electrophoresis, urine protein electrophoresis, immunofixation electrophoresis as well serum free light chains and their ratio, which helps clinicians identify any monoclonal paraproteinemia or Bence Jones proteinuria. Moreover, cardiac biomarkers troponins T and I, pro-BNP (brain type natriuretic peptide) and N-terminal pro-BNP, all serve as prognostic markers, and are frequently ordered. Other diagnostic modalities commonly used include EKG, echocardiography (ECHO), and cardiac magnetic resonance imaging (CMR). Eventually, to establish a tissue diagnosis demonstration of amyloid deposits in tissues is needed and for this purpose extra-cardiac biopsy (ex. fat pad biopsy), and or endomyocardial biopsy (gold standard) is needed. On EKG, patients with advanced cardiac amyloidosis can often have diffuse low voltage (Fig. 2) which is not specific for cardiac amyloidosis or other infiltrative cardiomyopathy as this can be seen in advanced emphysema, thick chest wall or in a case of pericardial effusion. Moreover, evidence of pseudo-infarction, which manifests as pathologic q waves (often in the chest leads, Fig. 2), is frequently seen in the absence

of a history of previous myocardial infraction or wall motion abnormality [10, 12]. Various arrhythmias are also frequently detected on EKG. Additionally, an ECHO is usually recommended for all patients with suspected amyloidosis. Patients with cardiac amyloidosis were found to have nonspecific findings as a thickened ventricle, left atrial enlargement, diastolic dysfunction, valve and intra-atrial septal thickening as well as a classic granular appearance on ECHO [12]. The CMR is in general more sensitive than ECHO and frequently used to assess the severity of the disease and has the potential for detection of amyloid cardiomyopathy earlier than can be detected by ECHO. CMR however is more technically demanding, expensive and not widely available and may have contraindication for example due to presence of cardiac pacemaker. Besides all the above diagnostic modalities, endomyocardial biopsy remains the gold standard (Fig. 1). Several life-threatening rhythmic abnormalities were frequently identified in patients with cardiac amyloidosis. These include ventricular tachycardia, ventricular fibrillation, pulseless electrical activity, atrial fibrillation as well as atrial flutter. The arrhythmias were commonly identified as a cause of sudden cardiac death in patients with cardiac amyloidosis.

The Mayo prognostic model involves a set of criteria that are frequently used for risk stratification, staging and prognostication of cardiac amyloidosis. It involves the use of NT pro-BNP as well as cardiac troponin levels (troponin T or I). However, a recent revision of the model incorporated markers of the plasma cell clone in the form of difference in the free light chain levels. Of interest, the difference between the involved and the uninvolved free light chains was found to have a significant influence on prognosis. Using this model, patients were stratified into 4 stages: stages I (no factor present), II (one factor present), III (two factors present), and IV (all three factors present) with a median survival of 94.1 months, 40.3 months, 14 months and 5.8 months respectively [13]. Given the importance of cardiac biomarkers in disease staging, risk stratification and prognosis of AL cardiomyopathy, most of the times the patient's clinical outcome depends on presence or absence of cardiac involvement [13, 14].

Treatment and supportive care

During the past decade, timely interventions have improved survival. Nevertheless, the continuous need to improve survival in this population was met by supportive care. As previously discussed, patients with cardiac amyloidosis frequently present with symptomatic heart failure. However, medications such as beta blockers, angiotensin converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARB), which are considered standard treatment in heart failure, are frequently avoided in patients with cardiac amyloidosis. These medications are poorly tolerated in this subset of patients because they tend to aggravate hypotension. Moreover, beta blockers were found to suppress sinus tachycardia which serves as a compensatory physiological mechanism. Similarly, the use of calcium channel blockers (e.g., diltiazem) was found to significantly worsen congestive heart failure in these patients and are therefore avoided. Clinicians should also refrain from using digoxin since it hasn't shown any benefit in this subset of patients and furthermore, digoxin can bind to amyloid fibrils and cause digoxin toxicity [15]. Therefore, the use of a combination of loop diuretics (mainly furosemide or torsemide) and aldosterone antagonists (e.g., spironolactone) has been the mainstay of treatment. Patients receiving these medications are closely monitoring for tolerance, large volume shifts leading to intravascular volume depletion, pre-renal azotemia and dyselectrolytemia induced by diuretics (e.g., hyponatremia, hypokalemia and hypomagnesemia) [6, 7]. Amyloid deposits in the conduction system of the heart can trigger various supraventricular and ventricular arrhythmias including sick sinus syndrome and various degree of heart blocks. Among the various available antiarrhythmic drugs, only amiodarone and (occasionally dofelitide) are tolerated and are therefore recommended for treatment of arrythmias. However, the use of anti-arrhythmic drugs did not show any survival benefit when prophylactically used [16]. As for transcatheter ablation, there is currently no evidence supporting its use as a first choice in treatment of supraventricular and ventricular arrhythmias due to the high incidence of recurrence. In one study 35% of patients with cardiac amyloidosis were found to have intracardiac thrombi [17]. Consequently, systemic thromboembolism has been identified as a common complication of AL amyloidosis. Anticoagulation with warfarin or newer oral anticoagulant such as rivaroxaban, apixaban and dabigatran can be considered in the setting of atrial fibrillation or atrial flutter or in the presence of left atrial mechanical dysfunction or presence of left atrial thrombus on ECHO. The risk and the benefits of anticoagulation should be individualized in systemic AL amyloidosis patients with history of or tendency of bleeding.

Finally, cardiac transplantation should be only considered in younger patients with isolated cardiac disease and in whom systemic chemotherapy is too toxic. If a cardiac transplantation is required, an induction regimen should be initiated to decrease circulating amyloidogenic light chain burden but post-transplant induction therapy and post-heart transplant HSCT can be considered for selected cases [18]. Keeping in mind toxicity from bortezomib-based induction regimens should be titrated and dose-adjusted. Now we have level 1 evidence from a large, randomized phase III ANDROMEDA clinical trial to use CyBorD plus daratumumab as the preferred induction regimen for treatment of systemic AL amyloidosis [19]. With orthotopic heart transplant, an overall survival of almost 90% at 1 year and 60% at 5 years has been reported in case series [20]. Here it is worth noting that despite the high survival rates, progression of the plasma cell dyscrasia puts the patient at risk of organ rejection or organ progression [21].

RENAL INVOLVEMENT IN AL AMYLOIDOSIS

Clinical picture

In patients with AL amyloidosis, amyloid fibrils deposit around 70 to 80% of cases in the kidneys which makes the kidney the most frequently involved organ [22]. Since these fibrils deposit in the glomeruli, proteinuria (predominantly albuminuria in the urine protein electrophoresis) is usually found in most patients and around 67% of cases progress to nephrotic syndrome. The typical presentation would be a patient with edema due to hypoalbuminemia, a hypercoagulable state (deep vein thrombosis and venous thromboembolic diseases) due to the loss of antithrombin III, a recent increase in infection rate due to the loss of IgG (acquired hypogammaglobulinemia) and varying degree of fluid overload ranging from modest peripheral edema to severe anasarca including genital edema, ascites and pleuropericardial effusion. Patients are also at risk for cellulitis from secondary skin infection due to marked skin edema particularly in the dependent parts of the body. A marked increase in triglycerides, cholesterol levels, and low-density lipoproteins puts the patient at high risk for accelerated atherosclerosis and marked increase in cardiovascular events such as myocardial infarction and stroke. There is also an increased resistance to hypolipidemic drugs making hyperlipidemia resistant to therapy. On the other side, rapidly progressive renal failure is only seen infrequently with only 20% of patients having a serum creatinine level higher than 2 mg/dL at the time of presentation.

Treatment and supportive care

Steroids (typically high dose dexamethasone and less commonly prednisone) are required for the prevention of infusion reactions and to achieve the maximum anti-plasma cell therapeutic effects of treatment regimens for AL amyloidosis [23-25]. Unfortunately, steroids also cause sodium and water retention exacerbating the anasarca and edema. Strict fluid and salt restriction along with use of loop diuretics are the mainstay of treatment of this condition. In the setting of severe hypoalbuminemia, intravenous 25% albumin may help alleviate edema and hypotension in very symptomatic hospitalized patients with fluid overload. This intervention is limited by high cost and lack of wide availability of 25% albumin. Prophylactic anticoagulation may be considered in low bleeding risk patients with serum albumin levels <20 g/L to cutdown the risk of venous thromboembolism [26]. Renin-angiotensin system (RAS) blockers should be held in patients with hypotension due to significant cardiac or autonomic nervous system involvement [27]. The role of RAS blockers is somewhat vague since even though they are used to minimize proteinuria in diabetic nephropathy, their role in AL amyloid nephropathy isn't yet justified [27]. In general, RAS blockers are contraindicated unless in a rare hypertensive patient with AL amyloid nephropathy. Such use should be collaborated with a nephrologist well versed in the management of AL amyloidosis patients (ideally in a collaboration with a nephro-oncologist). If the need to utilize them arises, short-acting ones at low doses are preferred. In extreme situations where patients remain hypotensive despite exhausting all methods, bilateral renal artery embolization can be considered but their routine use should be discouraged given the complexity of the procedure and risk of acute renal failure [28]. Given the importance of diuresis down to dry weight for the administration of anti-plasma cell therapy, patients are recommended to keep a log of weight gain of 1 kg or more over two days to the clinicians. Maintaining euvolemia through fluid restriction to $\leq$1.5 L/d or salt restriction to 1,500 to 200 mg/d is recommended. Patients should avoid high protein diets, which would exacerbate hypervolemia and induce glomerular hyperfiltration [29]. Anti-plasma cell therapy is the most effective therapy against glomerular proteinuria but the response is gradual and lags behind the hematologic response [30]. Renal response can be expected anywhere between 4 to 16 months after hematologic response has been achieved after initiating therapy. Volume depletion (e.g., due to overdiuresis), administration of intravenous contrast dyes or nephrotoxic drugs can exacerbate renal function and all effort should be made to avoid them.

According to Gertz *et al.* [9], almost 15% of patients progress to end-stage renal disease (ESRD). Based on a cutoff of proteinuria around 5 g/24 h and estimated glomerular filtration rate of 50 mL/min, renal staging system estimates renal outcomes. The decision to undergo renal replacement therapy however is estimated based on age, severity of extrarenal organ involvement and accessibility to anti-plasma cell rescue therapy [31]. First of all, no significant difference have been found between hemodialysis and peritoneal dialysis [32]. In general hemodialysis is considered inferior when it comes to quality of life achieved, but it is preferred for use in patients with severe hypoalbuminuria due to presence of ascites, peritoneal dialysis-related albumin loss or those at risk of peritonitis [32, 33]. Vascular access for hemodialysis may lead to higher risk of bleeding diatheses and arteriovenous fistula isn't always possible due to vascular and cutaneous amyloid deposition leading to skin and vascular fragility. Hemodialysis associated hypotension is a common occurrence in systemic AL amyloidosis patients who tend to run a borderline low blood pressure as the baseline. This can be overcome by administering midodrine before dialysis particularly in patients with coexisting cardiac or autonomic dysfunction. Because of the frequently coexisting cardiac amyloidosis, dialysis in the setting of ESRD due to renal amyloidosis is not associated with survival as promising as dialysis in the setting of other renal diseases [34].

Last, in cases where there is no concurrent renal and cardiac involvement, renal transplantation can be considered. Overall survival and dialysis-free survival were increased in four small series of patients who received high-dose melphalan around the time of stem cell rescue (HSCT) along with kidney transplantation [35-38]. HSCT is typically performed 6 to 12 months after the solid organ transplant because by then patients' performance status is improved and they

are likely to tolerate HSCT better. Antirejection prophylaxis with immunosuppression is usually continued through the stem cell mobilization, collection, and transplantation. Now, with the approval of highly effective anti-plasma cell therapy with CyBorD plus daratumumab in March of 2021, it is unclear if HSCT is still needed in patients with good performance status. Daratumumab based therapy is highly effective and is well tolerated by in patients with systemic AL amyloidosis who have undergone solid organ transplants [39]. Two things should be kept in mind here. First, amyloid fibrils' avidity for the transplanted organs is lower compared to the previous tropism for the native kidney [40]. Second, recurrence of amyloidosis can occur in the graft, but this can be tackled by administration of anti-plasma cell therapy with CyBorD plus sub-cutaneous daratumumab chemo-immunotherapy [40].

NEUROPATHY IN AL AMYLOIDOSIS

Clinical picture

Peripheral neuropathy associated with AL amyloidosis is one of the symptoms which rarely improves despite achieving a good hematological response. Almost 20% of patients develop painful symmetric and progressive numbness and paresthesia affecting the lower limbs [6]. The second most common complaint, seen 15% of the times, is symptoms associated with autonomic neuropathy such as orthostatic hypotension.

Treatment and supportive care

In general, treatment of peripheral neuropathy is mainly supportive and consists of anti-convulsants, gabapentin and pregabalin, and serotonin-norepinephrine reuptake inhibitors, duloxetine, and venlafaxine. Some topical agents such as lidocaine, ketamine and capsaicin are sometimes used. Drugs which aggravate concurrent autonomic symptoms are not recommended. These drugs include but are not limited to amitriptyline and nortriptyline. When it comes to autonomic neuropathy, compressive stockings can increase venous return and reduce peripheral edema. It goes without saying that a review of the active medications should be done. Common antihypertensive such as diuretics, nitrates and beta blockers along with other drugs which aggravate hypotension such as tamsulosin, tricyclics and antidepressants should either be eliminated or tapered to attain an acceptable blood pressure [41]. Midodrine can be given orally at a starting dose of 2.5 mg three time a day and escalated up to a maximum dose of 10 mg three times a day in order to avoid adverse events such as supine hypotension and tachycardia [42]. In rare cases where there is no cardiac involvement or overt proteinuria, salt tables or fludrocortisone can be utilized. Novel medications such as pyridostigmine and droxidopa can also be considered [43]. Maximal efforts should be done to prevent falls in elderly due to orthostatic hypotension. All patients should avoid prolonged periods of standing, and male patients in specific should sit while urinating. The main goal remains to find the right balance between fluid depletion on one end and volume overload on the other. Last, one complication from autonomic neuropathy that might arise is urinary tract dysfunction. For that reason, scheduled voiding and the Crede maneuver should be incorporated early on as part of the behavioral therapy recommended for patients [44]. If primary methods fail, scheduled self-catheterization may be required [45].

GASTROINTESTINAL AND HEPATOBILIARY OUTCOMES IN AL AMYLOIDOSIS

Clinical picture

Gastrointestinal hemorrhage, malabsorption and weight loss are the three most common presenting symptoms involving the alimentary tract. These can result from either autonomic dysfunction or amyloid deposition. The former, the more frequent cause of symptoms, has a wide variety of symptoms ranging from gastroparesis, post prandial fullness, constipation and diarrhea [46]. Dysmotility is noticeable at the proximal level of the GI tract as well. Achalasia, esophageal spasms, dysphagia and gastroesophageal reflux disease have been reported [47, 48]. Of the 8% of patients which have clinically significant GI tract involvement, 25% have hepatic involvement consisting of an increased serum alkaline phosphatase and palpable hepatomegaly [49]. On the contrary, only 5% of patients complain of splenomegaly. Among those affected, the initial manifestation of the disease was spontaneous rupture along with hypovolemic shock, and later findings include hyposplenism. Some patients have Howell-Jolly bodies in peripheral blood smears [22]. Last, cholestatic jaundice, which is associated with a median survival of $\leq$1 month, is the least common finding. This occurs in only 2% of patients [50].

Treatment and supportive care

In patients with motility disturbances, metoclopramide or loperamide can be used for constipation and diarrhea respectively. In patients with concurrent cardiac amyloidosis, QT prolongation should be considered. Constipation can also be managed by homogenized meals, sodium docusate, senna, and occasional judicious use of osmotic laxative. Severe fecal impaction can be treated with fluoroscopy-guided stool decompression or manual disimpaction. Diarrhea can also be managed by adding fiber to the diet and stool bulk forming agents. In patients who are refractory the aforementioned methods, bile acid binder or subcutaneous octreotide can be used [51, 52]. A swallowing evaluation is recommended in dysphagic patients. In case aspiration is present, swallowing rehabilitation is suggested. Most amyloid related dysphagia is resolved with dietary modification to thickened liquids. Rifaximin can be used for gastroparesis-induced small intestinal bacterial overgrowth. A limited tolerance to chemotherapy may arise, for that reason early nutritional support is needed. Dietitians, clinical nutritionists, and other special-

ists should be consulted. In the setting of chronic diarrhea, mineral and vitamin deficiencies may occur. Total parenteral nutrition can be used in select cases. Patients with cardiac amyloidosis should be monitored whilst on artificial nutrition due to their fluctuating volume status. In patients with extreme gastrointestinal bleeding, surgical resection is a serious option [53]. Platelet transfusions should be given for patients with GI bleeding during HSCT. A diverting ostomy has been done in cases of refractory diarrhea, and it has been reported to improve patients' quality of life [51, 54]. In cases where the spleen is involved, anti-pneumococcal vaccination is recommended.

PULMONARY INVOLVEMENT IN AL AMYLOIDOSIS

Clinical picture

Given that chemotherapy is only recommended in systemic disease, careful observation is required to distinguish between localized and systemic pulmonary disease. In systemic disease with pulmonary involvement, different patterns can be found upon presentation: diffuse, nodular, pleural, and diaphragmatic disease. In patients with localized disease, a nodular vs. trachea-bronchial disease is usually seen.

Treatment

In cases of systematic disease, supportive care including the optimization of filling pressures, serial drainage of pleural fluid and pleurodesis is required [55, 56]. Patients with localized disease are treated based on the severity of the disease in case a trachea-bronchial pattern is observed. Laser option, low-dose external beam radiation are viable options [57, 58]. Minimal bronchoscopies when undergoing any invasive, whether diagnostic or therapeutic, interventions are recommended to avoid scar stenosis. In certain situations, mucolytic agents, prophylactic antimicrobials, and nebulizers can be utilized in order to maintain airway patency and decrease the risk of infections [55].

COAGULATION IN AL AMYLOIDOSIS

Clinical picture

Combined severe deficiencies of two coagulation factors, IX and X, can be observed in patients with systemic AL amyloidosis. Around 15% of patients only have an acquired factor X deficiency. These patients often present with acute bleeds sometimes involving the mucosa [59-61]. To note, baseline factor X is not predictive of bleeding risk in this subset of patients. In case of vascular interventions, such as a central venous catheter placement or A-V fistula placement, patients are at an increased risk of post-intervention bleeding [62]. It should be kept in mind that the cutaneous easy bleeding or bruising (Fig. 3) is usually due to microcirculation fragility from amyloid deposits rather than underlying coagulopathy.

Treatment and supportive care

The main approach in the setting of bleeding is to achieve homeostasis while awaiting disease remission for the factor deficiency to resolve. In acute or periprocedural settings, recombinant factor VIIa is given at appropriate doses based on the patient's coagulation parameters [62, 63]. Other viable treating options are prothrombin complex concentrate or recombinant human factor X [64-66]. In refractory cases, a splenectomy is required to reduce amyloid burden [67-69]. Clot stabilization for mucosal bleeds is achieved using tranexamic acid. Of note, both tranexamic acid and recombinant factor VIIa are associated with increased risk of thrombosis and therefore, the risk of thrombosis should be discussed with patients and clinical team.

PSYCHOLOGICAL STATUS IN AL AMYLOIDOSIS

Clinical picture

Patients face hardships in their activities of daily living and require assistance from the disabilities related to advanced amyloidosis organ dysfunctions. Work leave absences are required in instances for different reasons such as chemotherapy appointments and multiple clinic visits or more importantly due to unremitting symptoms. This places an extra burden on diseased patients in fulfilling their regular tasks at work or in having to manage their absences with a depleted number of days. In that sense, a financial burden also arises as patients are no longer able to work due the morbidity. Patients also have increased expenditures which include but

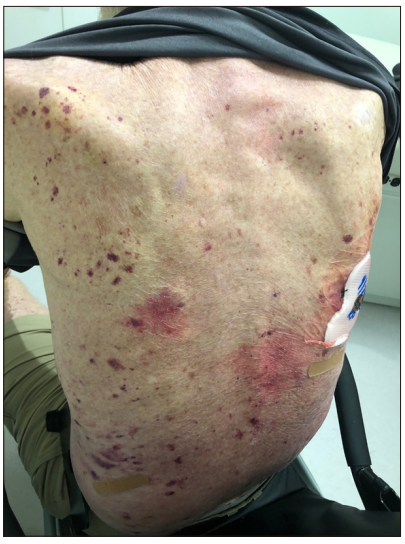

Fig. 3. One of the cutaneous manifestations of systemic AL amyloidosis include amyloid purpura. Amyloid purpura is non-blanching purpuric relapsing and remitting skin lesions usually involving the peri-orbital skin, the upper trunk and neck. The purpura can break and cause oozing, skin breakdown and significant pain. A marked thinning of skin and skin breakdown needing local care (for oozing and bleeding) is seen in the picture.

are not limited to travel cost, hospital admissions, copayments, and co-insurance for medications. To note, there is only one U.S. FDA approved regimen for AL amyloidosis (CyBorD+daratumumab), and other drugs approved for MM such as Immunomodulatory imide drugs (IMiDs) when used may not always be approved by insurance [7]. Some patients have reported that they have felt a sort of social isolation due to their decreased social interactions. This may be more relevant and likely much more prevalent in the era of COVID-19 pandemic. Patients have imposed social distancing due to their fear of infection while on chemotherapy; some were weak due to their symptoms. Significant others or close friends should be prepared to undergo the role of caregivers [70]. Similar to other incurable diseases, patients face an identity shift and slip into anxiety, despair, sadness, and hopelessness [71]. Patients recently diagnosed need support in overcoming psychological barriers related to the loss of well-being and health.

Treatment and supportive care

Regular psychological assessments may be needed at every patient encounter. Upon diagnosis, clinicians should go over advanced directives and goals of care with the patient and healthcare proxy. A social worker and a clinical psychologist should be consulted to meet psychosocial needs. Situational depression and anxiety related to amyloidosis, or its therapy can respond well to scheduled regular psychotherapy. Recurrent goal alignments between the providing physician and the patient should be done at timely intervals. Palliative care and hospice care are eventually utilized and facilitate patients' experience. In many cases, treatment might be difficult to tolerate and even worsen morbidity [71]. The burden of disease and burden of therapy should be carefully reviewed, followed up and managed by clinicians.

ENDOCRINOLOGICAL INVOLVEMENT IN AL AMYLOIDOSIS

Clinical picture

Nearly 50% of patients present with either submandibular gland enlargement or macroglossia. The latest studies have recommended screening for thyroid disease in recently diagnosed patients with AL amyloidosis. For that reason, thyroid-stimulating hormone levels should be obtained upon diagnosis, and this should be followed up by routine screening [72, 73]. Amyloid deposition in the submandibular gland, which is one of the largest salivary glands, can cause xerostomia, which is one of the earliest manifested symptoms [73]. In cases of macroglossia, patients can have obstructive sleep apnea, speech abnormalities, swallowing difficulties and airway obstruction in extreme cases.

Treatment and supportive care

In cases of xerostomia, factors that exacerbate this condition should be discontinued. These include but are not limited to smoking, caffeine intake, chewing tobacco. Like patients with Sjogren's syndrome, patients are at increased risk for dental caries. As part of dental care, patients should be started on artificial saliva for mouth lubrication, or/and sugarless gums and sialagogues to promote saliva production [73]. Topical fluoride to prevent tooth decay, the addition of remineralizing agents, and chlorhexidine antimicrobial rinses are recommended in cases which progress [74]. Follow ups with a dentist for regular checkups are recommended. In cases of macroglossia, some clinicians recommend surgical management while others prefer a tracheostomy with gastrostomy tube [75]. Some patients have benefited from the use of steroids. External beam radiation is not recommended due to lack of benefit [76]. Unfortunately, macroglossia can progress despite a good hematologic response.

MUSCULOSKELETAL AND DERMATOLOGICAL INVOLVEMENT IN AL AMYLOIDOSIS

Clinical picture

The most common musculoskeletal presentation in AL amyloidosis is carpal tunnel syndrome followed by amyloid arthropathy. The latter has been reported in less than 4% of patients and presents as nonerosive symmetric polyarthritis most frequently involving the shoulders followed by the hips, knees, wrist, elbows and interphalangeal joints [72]. The joints, periarticular structures and bones are the most affected structures. In rare instances, amyloidomas, which are tumors formed by amyloid deposits, can be in bones, soft tissues, or joints. Some retroperitoneal and mediastinal masses have been reported as well.

Other typical symptoms caused by amyloid deposition are petechia, purpura, and ecchymoses (Fig. 2). When amyloid deposits infiltrate the blood vessels, skin bullae and increased skin fragility are observed [77, 78]. This can lead to non-healing painful ulcer at the pressure points such as sacral area in a bedbound patient.

Treatment and supportive care

Concerning carpal tunnel syndrome, the treatment approach is like carpal tunnel caused by non-amyloid etiologies. Wrist guards, supportive care, and eventual surgical release are plausible options. In a study done by Elsaman *et al.* [79], anti-inflammatory drugs or intra-articular corticosteroid injections were effective in patients with amyloid arthropathy with concurrent MM. Some patients also benefited from radiosynovectomy. Despite achieving good hematologic response, patients had amyloid arthropathy and necessitated the previously mentioned therapeutic methods. Concerning amyloidomas, surgical excision is recommended in symptomatic patients. Concerning cases of bullous amyloidosis, nurses and practitioners should use paper tape as silk tape is harmful due to skin fragility. Chronic topical steroid use should be limited to a maximum of only 6 days due to skin fragility as well [78].

CONCLUSION

Detection of different disease manifestations in various organ should be kept in mind in patients with systemic AL amyloidosis. Anti-plasma cell therapy along with supportive measures should be established as soon as a diagnosis is made. Appropriate chemotherapy administration should be done with the hope of achieving hematologic response. Now with the availability of daratumumab +CyBorD, most patients with advanced disease who are not candidate for upfront HSCT, can be treated with this highly effective and tolerable regimen. In most organ systems (particularly heart), a good hematologic response usually projects a good organ specific response. In other organ systems, such as the kidneys, more interventions are needed. Despite advances in the anti-plasma cell therapy, advanced amyloid cardiomyopathy remains a major cause of AL amyloidosis related death. There is an unmet need for novel agents that help rapid removal of amyloid from vital organs and help translate hematologic response into organ response before the patient dies. Hopefully in near future, the anti-amyloid fibrils monoclonal antibodies currently in phase III clinical trials (CAEL-101 and birtamimab) will be able to fill this gap and help rescue very sick patients particularly those with stage IIIb/stage IV cardiac AL amyloidosis. To achieve a maximal organ response and minimize symptom burden, a multidisciplinary approach should be utilized. Apart from primary physicians, social workers, psychologists, dentists, and different specialists (particularly cardio-oncologists and nephro-oncologitsts) should be involved in the management of this heterogeneous disease.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Cook J, Muchtar E, Warsame R. Updates in the diagnosis and management of AL amyloidosis. Curr Hematol Malig Rep 2020;15:155-67.
2. Ryšavá R. AL amyloidosis: advances in diagnostics and treatment. Nephrol Dial Transplant 2019;34:1460-6.
3. Gertz MA. Immunoglobulin light chain amyloidosis: 2018 update on diagnosis, prognosis, and treatment. Am J Hematol 2018;93:1169-80.
4. Quock TP, Yan T, Chang E, Guthrie S, Broder MS. Epidemiology of AL amyloidosis: a real-world study using US claims data. Blood Adv 2018;2:1046-53.
5. Joseph NS, Kaufman JL. Novel approaches for the management of AL amyloidosis. Curr Hematol Malig Rep 2018;13:212-9.
6. Cibeira MT, Ortiz-Pérez JT, Quintana LF, Fernádez de Larrea C, Tovar N, Bladé J. Supportive care in AL amyloidosis. Acta Haematol 2020;143:335-42.
7. Wong SW, Fogaren T. Supportive care for patients with systemic light chain amyloidosis. Hematol Oncol Clin North Am 2020;34:1177-91.
8. Khouri J, Anwer F, Samaras CJ, et al. Safety, tolerability and efficacy of Cael-101 in AL amyloidosis patients treated on a phase 2, open-label, dose selection study to evaluate the safety and tolerability of Cael-101 in patients with AL amyloidosis. Blood (ASH Annual Meeting Abstracts) 2020;136(Suppl):21.
9. Gertz MA, Landau H, Comenzo RL, et al. First-in-human phase I/II study of NEOD001 in patients with light chain amyloidosis and persistent organ dysfunction. J Clin Oncol 2016;34:1097-103.
10. Rubin J, Maurer MS. Cardiac amyloidosis: overlooked, underappreciated, and treatable. Annu Rev Med 2020;71:203-19.
11. Falk RH, Alexander KM, Liao R, Dorbala S. AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy. J Am Coll Cardiol 2016;68:1323-41.
12. Bhogal S, Ladia V, Sitwala P, et al. Cardiac amyloidosis: an updated review with emphasis on diagnosis and future directions. Curr Probl Cardiol 2018;43:10-34.
13. Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol 2012;30:989-95.
14. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol 2004;22:3751-7.
15. Muchtar E, Gertz MA, Kumar SK, et al. Digoxin use in systemic light-chain (AL) amyloidosis: contra-indicated or cautious use? Amyloid 2018;25:86-92.
16. Ashraf I, Peck MM, Maram R, et al. Association of arrhythmias in cardiac amyloidosis and cardiac sarcoidosis. Cureus 2020;12:e9842.
17. Feng D, Syed IS, Martinez M, et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. Circulation 2009;119:2490-7.
18. Ton K, Watts J, Malhotra R, et al. Predictors of survival to orthotopic heart transplant in patients with immunoglobulin light chain amyloid cardiomyopathy. Circulation 2011;124(Suppl):A18160.
19. Palladini G, Kastritis E, Maurer MS, et al. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. Blood 2020;136:71-80.
20. Griffin JM, Chiu L, Axsom KM, et al. Outcomes after heart transplantation for AL compared to ATTR cardiac amyloidosis. Clin Transplant 2020;34:e14028.
21. Qualls DA, Lewis GD, Sanchorawala V, Staron A. Orthotopic heart transplant rejection in association with immunomodulatory therapy for AL amyloidosis: a case series and review of the literature. Am J Transplant 2019;19:3185-90.
22. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol 1995;32:45-59.
23. Palladini G, Milani P, Foli A, et al. Melphalan and dexamethasone with or without bortezomib in newly diagnosed AL amyloidosis: a matched case-control study on 174 patients. Leukemia 2014;28:2311-6.
24. Roussel M, Merlini G, Chevret S, et al. A prospective phase 2 trial

of daratumumab in patients with previously treated systemic light-chain amyloidosis. Blood 2020;135:1531-40.
25. Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood 2015;126:612-5.
26. Lee T, Biddle AK, Lionaki S, et al. Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy. Kidney Int 2014;85:1412-20.
27. Gentile G, Remuzzi G, Ruggenenti P. Dual renin-angiotensin system blockade for nephroprotection: still under scrutiny. Nephron 2015;129:39-41.
28. Yeh CT, Tseng HS, Liu WS, Li SY, Yang WC, Ng YY. Severe proteinuria secondary to amyloidosis requiring bilateral renal artery embolization. Case Rep Nephrol Urol 2012;2:78-82.
29. Friedman AN. High-protein diets: potential effects on the kidney in renal health and disease. Am J Kidney Dis 2004;44:950-62.
30. Pinney JH, Lachmann HJ, Bansi L, et al. Outcome in renal AL amyloidosis after chemotherapy. J Clin Oncol 2011;29:674-81.
31. Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood 2014;124:2325-32.
32. Moroni G, Banfi G, Montoli A, et al. Chronic dialysis in patients with systemic amyloidosis: the experience in northern Italy. Clin Nephrol 1992;38:81-5.
33. Kagan A, Bar-Khayim Y. Role of peritoneal loss of albumin in the hypoalbuminemia of continuous ambulatory peritoneal dialysis patients: relationship to peritoneal transport of solutes. Nephron 1995;71:314-20.
34. Gertz MA, Kyle RA, O'Fallon WM. Dialysis support of patients with primary systemic amyloidosis. A study of 211 patients. Arch Intern Med 1992;152:2245-50.
35. Sattianayagam PT, Gibbs SD, Pinney JH, et al. Solid organ transplantation in AL amyloidosis. Am J Transplant 2010;10: 2124-31.
36. Herrmann SM, Gertz MA, Stegall MD, et al. Long-term outcomes of patients with light chain amyloidosis (AL) after renal transplantation with or without stem cell transplantation. Nephrol Dial Transplant 2011;26:2032-6.
37. Angel-Korman A, Stern L, Sarosiek S, et al. Long-term outcome of kidney transplantation in AL amyloidosis. Kidney Int 2019; 95:405-11.
38. Sathick IJ, Rosenbaum CA, Gutgarts V, Landau H. Kidney transplantation in AL amyloidosis: is it time to maximize access? Br J Haematol 2020;188:e1-4.
39. Chaulagain CP, Diacovo JM, Elson L, et al. Daratumumab-based regimen in treating clonal plasma cell neoplasms in solid organ transplant recipients. Clin Lymphoma Myeloma Leuk 2020;20: e137-43.
40. Ow SY, Dunstan DE. A brief overview of amyloids and Alzheimer's disease. Protein Sci 2014;23:1315-31.
41. Freeman R, Abuzinadah AR, Gibbons C, Jones P, Miglis MG, Sinn DI. Orthostatic hypotension: JACC state-of-the-art review. J Am Coll Cardiol 2018;72:1294-309.
42. Weber N, Mollee P, Augustson B, et al. Management of systemic AL amyloidosis: recommendations of the Myeloma Foundation of Australia Medical and Scientific Advisory Group. Intern Med J 2015;45:371-82.
43. Freeman R. Clinical practice. Neurogenic orthostatic hypotension. N Engl J Med 2008;358:615-24.
44. Andrade MJ. Lower urinary tract dysfunction in familial amyloidotic polyneuropathy, Portuguese type. Neurourol Urodyn 2009;28:26-32.
45. Burakgazi AZ, Alsowaity B, Burakgazi ZA, Unal D, Kelly JJ. Bladder dysfunction in peripheral neuropathies. Muscle Nerve 2012;45:2-8.
46. Wixner J, Suhr OB, Anan I. Management of gastrointestinal complications in hereditary transthyretin amyloidosis: a single-center experience over 40 years. Expert Rev Gastroenterol Hepatol 2018;12:73-81.
47. Rubinow A, Burakoff R, Cohen AS, Harris LD. Esophageal manometry in systemic amyloidosis. A study of 30 patients. Am J Med 1983;75:951-6.
48. Battle WM, Rubin MR, Cohen S, Snape WJ Jr. Gastrointestinal-motility dysfunction in amyloidosis. N Engl J Med 1979;301:24-5.
49. Menke DM, Kyle RA, Fleming CR, Wolfe JT 3rd, Kurtin PJ, Oldenburg WA. Symptomatic gastric amyloidosis in patients with primary systemic amyloidosis. Mayo Clin Proc 1993;68:763-7.
50. Park MA, Mueller PS, Kyle RA, Larson DR, Plevak MF, Gertz MA. Primary (AL) hepatic amyloidosis: clinical features and natural history in 98 patients. Medicine (Baltimore) 2003;82:291-8.
51. Gertz MA, Lacy MQ, Dispenzieri A. Therapy for immunoglobulin light chain amyloidosis: the new and the old. Blood Rev 2004; 18:17-37.
52. Yam LT, Oropilla SB. Octreotide for diarrhea in amyloidosis. Ann Intern Med 1991;115:577.
53. Rives S, Pera M, Rosiñol L, et al. Primary systemic amyloidosis presenting as a colonic stricture: successful treatment with left hemicolectomy followed by autologous hematopoietic stem-cell transplantation. Dis Colon Rectum 2002;45:1263-6.
54. Ek BO, Holmlund DE, Sjödin JG, Steen LE. Enterostomy in patients with primary neuropathic amyloidosis. Am J Gastroenterol 1978;70:365-70.
55. Berk JL, O'Regan A, Skinner M. Pulmonary and tracheobronchial amyloidosis. Semin Respir Crit Care Med 2002;23:155-65.
56. Baumgart JV, Stuhlmann-Laeisz C, Hegenbart U, et al. Local vs. systemic pulmonary amyloidosis—impact on diagnostics and clinical management. Virchows Arch 2018;473:627-37.
57. Kurrus JA, Hayes JK, Hoidal JR, Menendez MM, Elstad MR. Radiation therapy for tracheobronchial amyloidosis. Chest 1998;114:1489-92.
58. Fiorelli A, Accardo M, Galluccio G, Santini M. Tracheobronchial amyloidosis treated by endobronchial laser resection and self expanding Y stent. Arch Bronconeumol 2013;49:303-5.
59. Ericson S, Shah N, Liberman J, Aboulafia DM. Fatal bleeding due to acquired factor IX and X deficiency: a rare complication of primary amyloidosis; case report and review of the literature. Clin Lymphoma Myeloma Leuk 2014;14:e81-6.
60. McPherson RA, Onstad JW, Ugoretz RJ, Wolf PL. Coagulopathy in amyloidosis: combined deficiency of factors IX and X. Am J Hematol 1977;3:225-35.
61. Gertz MA, Lacy MQ, Dispenzieri A. Amyloidosis: recognition, confirmation, prognosis, and therapy. Mayo Clin Proc 1999;74: 490-4.

62. Thompson CA, Kyle R, Gertz M, Heit J, Pruthi R, Pardanani A. Systemic AL amyloidosis with acquired factor X deficiency: a study of perioperative bleeding risk and treatment outcomes in 60 patients. Am J Hematol 2010;85:171-3.
63. Boggio L, Green D. Recombinant human factor VIIa in the management of amyloid-associated factor X deficiency. Br J Haematol 2001;112:1074-5.
64. Veneri D, Giuffrida AC, Bonalumi A, et al. Use of prothrombin complex concentrate for prophylaxis of bleeding in acquired factor X deficiency associated with light-chain amyloidosis. Blood Transfus 2016;14:585-6.
65. Litvak A, Kumar A, Wong RJ, Smith L, Hassou H, Soff G. Successful perioperative use of prothrombin complex concentrate in the treatment of acquired factor X deficiency in the setting of systemic light-chain (AL) amyloidosis. Am J Hematol 2014;89:1153-4.
66. Mahmood S, Blundell J, Drebes A, Hawkins PN, Wechalekar AD. Utility of factor X concentrate for the treatment of acquired factor X deficiency in systemic light-chain amyloidosis. Blood 2014; 123:2899-900.
67. Greipp PR, Kyle RA, Bowie EJ. Factor X deficiency in primary amyloidosis: resolution after splenectomy. N Engl J Med 1979; 301:1050-1.
68. Rosenstein ED, Itzkowitz SH, Penziner AS, Cohen JI, Mornaghi RA. Resolution of factor X deficiency in primary amyloidosis following splenectomy. Arch Intern Med 1983;143:597-9.
69. Böhrer H, Waldherr R, Martin E, et al. Splenectomy in an uraemic patient with acquired factor X deficiency due to AL amyloidosis. Nephrol Dial Transplant 1998;13:190-3.
70. Lin HM, Seldin D, Hui AM, Berg D, Dietrich CN, Flood E. The patient's perspective on the symptom and everyday life impact of AL amyloidosis. Amyloid 2015;22:244-51.
71. Lousada I, Comenzo RL, Landau H, Guthrie S, Merlini G. Light chain amyloidosis: patient experience survey from the amyloidosis research consortium. Adv Ther 2015;32:920-8.
72. Prokaeva T, Spencer B, Kaut M, et al. Soft tissue, joint, and bone manifestations of AL amyloidosis: clinical presentation, molecular features, and survival. Arthritis Rheum 2007;56: 3858-68.
73. Muchtar E, Derudas D, Mauermann M, et al. Systemic immunoglobulin light chain amyloidosis–associated myopathy: presentation, diagnostic pitfalls, and outcome. Mayo Clin Proc 2016;91:1354-61.
74. Vivino FB. Sjogren's syndrome: clinical aspects. Clin Immunol 2017;182:48-54.
75. Jacobs P, Sellars S, King HS. Massive macroglossia, amyloidosis and myeloma. Postgrad Med J 1988;64:696-8.
76. Thibault I, Vallières I. Macroglossia due to systemic amyloidosis: is there a role for radiotherapy? Case Rep Oncol 2011;4:392-9.
77. Eder L, Bitterman H. Image in clinical medicine. Amyloid purpura. N Engl J Med 2007;356:2406.
78. Westermark P, Ohman S, Domar M, Sletten K. Bullous amyloidosis. Arch Dermatol 1981;117:782-4.
79. Elsaman AM, Radwan AR, Akmatov MK, et al. Amyloid arthropathy associated with multiple myeloma: a systematic analysis of 101 reported cases. Semin Arthritis Rheum 2013;43: 405-12.