Amyloidosis is a rare disease process that results in the deposition of insoluble, fibrous amyloid proteins in extracellular spaces and tissues. Amyloid fibrils can be deposited locally or may involve every organ system of the body. Advances in the treatment for amyloidosis allow longer survival, and patients are being seen in our operating rooms for diagnostic, interventional, and curative purposes. Amyloidosis has numerous implications for anesthesia providers due to the possibility of systemic involvement. This course describes 2 cases of amyloidosis and discusses the types of amyloidosis and their anesthetic implications.

Key words: Amyloidosis, anesthesia, hemodynamics, sedation, transplant.

Objectives
At completion of this course, the reader should be able to:

1. Describe the disease process of amyloidosis.
2. Describe the complex symptoms and manifestations of amyloidosis that may involve every body organ and tissue.
3. Incorporate the anesthetic considerations into the care for a patient with amyloidosis.
4. Discuss stem cell transplantation and its use in treating amyloidosis.
5. Discuss the treatment options for primary and familial amyloidosis.

Introduction
Amyloidosis is a plasma cell dyscrasia with multiple anesthetic implications. Insoluble immunoglobulin deposits may involve virtually any organ system of the body, leading to severe pathophysiologic changes.1,2 This article describes 2 cases of amyloidosis and discusses the types of amyloidosis and anesthetic implications.

Case 1
A 46-year-old man was given a diagnosis of systemic amyloidosis. The patient began to experience fatigue, dyspnea, and chest pain, and had 3 syncopal episodes 14 months before initial examination. A diagnosis of cardiomyopathy was made at that time. Cardiac monitoring revealed runs of nonsustained ventricular tachycardia with mild hypotension. The patient had an arterial embolism in his right arm requiring an embolectomy and initiation of anticoagulant therapy. Throughout this period, the patient also experienced subconjunctival hemorrhages, voice changes, xerostomia, jaw claudication, decreased appetite, and weight loss.

The patient was referred to a tertiary center for treatment and consideration of heart transplantation. The electrocardiogram revealed premature ventricular complexes and a low-voltage QRS complex. An echocardiogram revealed normal left ventricular size and generalized left ventricular hypokinesis with an estimated ejection fraction of 40%. The ventricular septum and right and left ventricular walls were thickened, and there was diastolic dysfunction. The findings were considered consistent with amyloid heart disease. Cardiac catheterization revealed congestive cardiomyopathy and moderate pulmonary hypertension. A right-sided myocardial biopsy was performed.
and was positive for amyloid heart disease. A bone marrow biopsy revealed hypercellularity and 20% plasma cells in his bone marrow. An IgA lambda monoclonal protein was identified in his serum, and lambda light chains in his urine were consistent with a plasma cell dyscrasia. Pulmonary function tests revealed mild restrictive lung disease.

The patient underwent internal cardiac defibrillator placement due to several episodes of syncope with ventricular tachycardia. Cardiac transplantation was delayed in lieu of autologous stem cell transplantation to treat amyloidosis. In preparation for the stem cell transplantation, the patient underwent Hickman catheter placement without complications. This procedure was completed with sedation using midazolam and fentanyl.

Stem cell mobilization with granulocyte colony-stimulating factor was initiated 1 day after catheter placement. The granulocyte colony-stimulating factor causes the release of large numbers of peripheral blood stem cells into the bloodstream.* After stem cell mobilization, significant weight gain and worsening dyspnea developed. A thoracentesis was completed and provided symptomatic relief. The patient was hospitalized due to severe episodes of syncope and hypotension. He then underwent 12 days of stem cell collection. A repeated echocardiogram revealed severely impaired cardiac function with an ejection fraction of 10%. The patient died 23 days after initiation of stem cell transplantation.

Case 2

A 49-year-old man with a family history of type 1 familial amyloidosis sought care because of gastrointestinal complaints, peripheral neuropathy, and visual changes. Gastrointestinal symptoms included difficulty swallowing, abdominal cramps, nausea, and vomiting, with a 20-pound weight loss.

An electrocardiogram showed normal sinus rhythm with low-voltage QRS complex with anteroseptal and inferior infarcts. An echocardiogram revealed normal systolic function with a 60% ejection fraction; however, there was a marked increase in the left ventricular wall thickness. Diastolic dysfunction also was noted. DNA studies of the patient and 2 of his sisters were positive for a tyrosine 77 mutation, an amyloid precursor protein.2

The clinical findings suggested that this patient had autonomic neuropathy with gastrointestinal symptoms rather than amyloid deposition in the gastrointestinal tract. Autonomic neuropathy usually improves after transplantation, whereas peripheral neuropathy does not. Curative treatment for familial amyloidosis is liver transplantation.1,2,4-6 Even though the patient was asymptomatic from a cardiac standpoint, inadequate cardiac reserve during the liver transplantation period or progression of his cardiac disease despite liver transplantation was a concern. The patient was listed for heart and liver transplantation.

Heart transplantation occurred 1 year later. A liver transplant was not completed due to hemodynamic instability during the cardiac procedure. A right ventricular assist device and an intra-aortic balloon pump were required postoperatively for hemodynamic support. An echocardiogram on postoperative day 1 showed an ejection fraction of 35%. Serial echocardiograms revealed continued improvement to an ejection fraction of 65%, at which time the intra-aortic balloon pump was discontinued. The right ventricular assist device was weaned and removed without complications 1 week after transplantation. Dismissal echocardiogram results revealed a normal left ventricle with an estimated ejection fraction of 61%. The patient is being reevaluated for liver transplantation.

Discussion

Amyloidosis results from the deposition of insoluble, fibrous amyloid proteins in the extracellular spaces of organs and tissues. Depending on the biochemical nature of the amyloid precursor protein, amyloid fibrils can be deposited locally or may involve every organ system of the body. There are multiple forms of amyloid fibrils, which are classified according to the unique fibrous structure that they each possess. The following forms exist: (1) primary (AL) amyloidosis (no evidence of preexisting or coexisting disease); (2) amyloidosis associated with multiple myeloma (also the AL type); (3) secondary (AA) amyloidosis associated with chronic infectious diseases or chronic inflammatory diseases; (4) heredofamilial amyloidosis (AF); (5) local (AE) amyloidosis (amyloid deposition limited to a single organ); (6) senile (AS) associated with aging; (7) chronic hemodialysis–related amyloidosis (AH).2,6 (See Table 1.)

Amyloidosis is a rare disease, affecting about 8 persons per million annually. In patients with primary amyloidosis, 15% to 20% have AL associated with myeloma, 95% are older than 40 years, and 66% are

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* Stem cells are immature cells that grow and divide into mature red blood cells, white blood cells, or platelets. When the white blood cell count has increased to a sufficient level, stem cell collection begins. High-dose chemotherapy is a potential cure for this disease. However, high-dose chemotherapy suppresses bone marrow production of stem cells, and mobilized peripheral blood stem cells are needed to restore bone marrow function. Before the use of high-dose chemotherapy, peripheral blood stem cells are collected and frozen for storage. After chemotherapy, the peripheral blood stem cells are thawed and transfused into the patient. The stem cells migrate to the bone marrow and begin the process of creating new blood cells.3
The average survival with primary amyloidosis is 12 months, and in familial amyloidosis, survival is 7 to 15 years. The major causes of death are heart disease and renal failure. Sudden death, presumably due to arrhythmias, is common.

AL amyloidosis is a disease process in which a monoclonal population of bone marrow plasma cells produces small lambda or kappa fragments that are processed in an abnormal manner by macrophage enzymes. The enzymes produce the partially degraded light chains responsible for AL amyloidosis. The insoluble amyloid fibril, or light chain, deposits in the extracellular spaces of organs and tissues lead to organ failure and, eventually, death.

Primary amyloidosis related to multiple myeloma is a relatively rare disease with 3,000 cases reported annually in the United States. Multiple myeloma is a cancer of the plasma cells. Plasma cells, which are located in the bone marrow, function as part of the immune system by producing antibodies. Normal bone marrow contains only about 2% plasma cells. With multiple myeloma, increased abnormal plasma cells produce increased numbers of antibodies. These additional antibodies do not function normally and are thought to prevent the body from making normal infection-fighting antibodies.

Primary amyloidosis related to multiple myeloma is a rapidly progressive disease once symptoms occur, and life expectancy is usually less than 6 months. Diagnosis often is made late in the course of the disease, and cardiac failure is the most common initial symptom.

Familial amyloidosis involves a mutant transthyretin protein that forms amyloid fibrils, leading to polyneuropathy, cardiomyopathy, or both. The mutant proteins, although present from birth, are associated with a delayed onset of symptoms, usually after 3 to 7 decades of life. The amyloid fibrils are characterized by single amino acid substitutions within the transthyretin molecule. The liver produces transthyretin (normal or abnormal amyloid) almost exclusively; therefore, liver transplantation has been successful in the treatment of familial amyloidosis.

Anesthetic implications

The clinical manifestations of amyloidosis are varied and depend entirely on the area of the body that is involved. In many cases, amyloid fibrils deposit in the heart (Table 2). The myocardium involved with amyloid deposition is usually firm, thickened, and non-compliant, which can result in restrictive cardiomyopathy with systolic or diastolic impairment (Figures 1A and Figure 2). Cardiac manifestations consist primarily of congestive heart failure, cardiomegaly, and a variety of arrhythmias. Echocardiogram abnormalities include low-voltage QRS complex and conduction abnormalities, often resulting in varying degrees of heart block. Syncope is common and is a strong predictor of sudden death.

Anesthesia providers must be aware of the cardiac manifestations of amyloidosis and the associated implications. In patients with cardiac involvement, the reduced stroke volume due to diastolic dysfunction produces systolic hypotension. It can be difficult to maintain hemodynamic stability during induction and throughout the surgical period. The cardiac depressant effects of anesthetic drugs enhance amyloid-related dysfunction. The need for invasive monitoring and central venous access should be determined on a case-by-case basis.

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Table 1. Classification of amyloidosis

<table>
<thead>
<tr>
<th>Classification</th>
<th>Associated diseases</th>
<th>Chemically related precursor protein</th>
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</thead>
<tbody>
<tr>
<td>Primary amyloidosis</td>
<td>No evidence of preexisting or coexisting disease</td>
<td>Immunoglobulin kappa and lambda light chains</td>
</tr>
<tr>
<td>Primary amyloidosis related to multiple myeloma</td>
<td>Multiple myeloma</td>
<td>Immunoglobulin kappa and lambda light chains</td>
</tr>
<tr>
<td>Secondary/reactive</td>
<td>Chronic infections or inflammatory conditions</td>
<td>Serum amyloid A (SAA)</td>
</tr>
<tr>
<td>Heredofamilial</td>
<td>Genetically predisposed</td>
<td>Transthyretin (more than 50 known mutations)</td>
</tr>
<tr>
<td>Local</td>
<td>Deposits limited to a single organ</td>
<td>Amyloid proteins seem to be derived from polypeptide hormones or unique proteins</td>
</tr>
<tr>
<td>Senile</td>
<td>Alzheimer disease</td>
<td>Amyloid precursor protein (APP)</td>
</tr>
<tr>
<td>Chronic hemodialysis-related amyloidosis</td>
<td>Chronic renal failure</td>
<td>β₂-microglobulin</td>
</tr>
</tbody>
</table>

* Compiled from Wilson et al., Lee et al., and Kumar et al.
### Table 2. Systemic effects of amyloidosis*

<table>
<thead>
<tr>
<th>Body system</th>
<th>Manifestations</th>
<th>Anesthetic considerations for each body system</th>
</tr>
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<tbody>
<tr>
<td>Cardiac</td>
<td>Restrictive cardiomyopathy</td>
<td>Anesthetic plan according to cardiac dysfunction</td>
</tr>
<tr>
<td></td>
<td>Systolic or diastolic dysfunction</td>
<td>Hemodynamic challenges during induction and throughout the perioperative period</td>
</tr>
<tr>
<td></td>
<td>Cardiomegaly</td>
<td>Enhancement of amyloid-related dysfunction by the cardiac depressant effects of anesthetic drugs</td>
</tr>
<tr>
<td></td>
<td>Arrhythmias</td>
<td>Immediate availability of emergency drugs and defibrillator due to the risk of cardiac arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
<td></td>
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<td></td>
<td>Electrocardiogram: thickening of the left ventricular wall and interventricular septum, hypokinesia, and decreased systolic contraction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Echocardiogram: thickening of the left ventricular wall and interventricular septum, hypokinesia, and decreased systolic contraction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Electrocardiogram: low-voltage QRS complex with conduction abnormalities; heart blocks and arrhythmias common</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Range from proteinuria to nephrotic syndrome</td>
<td>Influence of impaired renal function on drug selection</td>
</tr>
<tr>
<td></td>
<td>Elevated creatinine level</td>
<td>Reduced protein binding of drugs</td>
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<tr>
<td></td>
<td>Hypoalbuminuria</td>
<td>Maintain perfusion pressure and adequate hydration.</td>
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<tr>
<td></td>
<td>Increased proteinuria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased renal function and renal blood flow</td>
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<tr>
<td>Respiratory</td>
<td>Larynx most common site in respiratory tract; amyloid deposits of tumors of masses or diffuse infiltration; signs and symptoms: hoarseness, dyspnea, and dysphagia</td>
<td>Thorough airway examination before any sedation or anesthetic: hoarseness, voice changes, enlarged or swollen tongue, dry mouth, difficulty breathing, and wheezing</td>
</tr>
<tr>
<td></td>
<td>Macroglossia</td>
<td>Macroglossia: patent airway obstruction and direct laryngoscopy interference</td>
</tr>
<tr>
<td></td>
<td>Salivary gland involvement</td>
<td>Difficult intubation; possible complications, airway obstruction and hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Possible blockage of ducts or the air passages in the nasal sinuses, larynx, and trachea by accumulation of amyloid fibrils</td>
<td>Prevention of airway obstruction and an unprotected airway if laryngeal or respiratory amyloidosis is diagnosed or suspected by careful titration of sedation</td>
</tr>
<tr>
<td></td>
<td>Progressive stenosis of the airways due to deposition of amyloid fibrils in the tracheobronchial tree</td>
<td>Difficulty with ventilation, wheezing, and/or bronchospasm due to airway stenosis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Gastrointestinal involvement common in all forms; occurs at all levels of the gastrointestinal tract. Symptoms: obstruction, hemorrhage, diarrhea, malnutrition, and dehydration</td>
<td>Proper intravenous hydration</td>
</tr>
<tr>
<td></td>
<td>Gastric reflux</td>
<td>Monitoring of electrolytes and hemoglobin</td>
</tr>
<tr>
<td></td>
<td>Delayed gastric emptying</td>
<td>Rapid-sequence induction</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Peripheral neuropathy</td>
<td>Neuropathy a relative contraindication to regional anesthesia</td>
</tr>
<tr>
<td></td>
<td>Autonomic neuropathy</td>
<td>Vigilant positioning to prevent nerve damage and further exacerbate neuropathies</td>
</tr>
<tr>
<td></td>
<td>Postural hypotension</td>
<td>Significant hypotension and delayed gastric emptying due to autonomic neuropathy</td>
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<tr>
<td></td>
<td>Carpal tunnel syndrome</td>
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<td></td>
<td>Visual changes</td>
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<td></td>
<td>Alzheimer disease</td>
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<tr>
<td>Skin</td>
<td>Raised waxy papules or plaques, usually in the face or neck or clustered in the folds of the axillary, anal, or inguinal regions; periorbital ecchymoses</td>
<td>Vigilant positioning to prevent skin breakdown</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Hematological changes: increased fibrinolysis and selective deficiency of clotting factors</td>
<td>Preoperative and perioperative monitoring of complete blood cell count, prothrombin time, activated partial thromboplastin time, international normalized ratio, and bleeding time</td>
</tr>
<tr>
<td></td>
<td>Acquired factor X deficiency</td>
<td></td>
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<tr>
<td></td>
<td>Hepatomegaly</td>
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</tbody>
</table>

* Compiled from entire list of references.1-11
by-case basis. Emergency drugs and a defibrillator should be immediately available due to the risk of cardiac arrhythmias and dysfunction.\textsuperscript{1,2,4,5} The cause of death in most patients with amyloidosis is cardiac—progressive cardiomyopathy with heart failure or sudden death due to ventricular arrhythmias.\textsuperscript{1,2,5,7,9}

Renal involvement is common and potentially the most serious manifestation of amyloidosis.\textsuperscript{5,7,9} Amyloid involvement in the kidney may range from mild proteinuria to nephrotic syndrome.\textsuperscript{1,2,7} Renal tubular acidosis and renal vein thrombosis may occur.\textsuperscript{1,2,5,7,9} Impaired renal function and clearance may influence drug selection.\textsuperscript{5}

The respiratory system and gastrointestinal tract are commonly affected by amyloidosis. The larynx is the most common site for amyloidosis in the respiratory tract. Symptoms consist mainly of hoarseness, but dyspnea and dysphagia may be present.\textsuperscript{11} The nasal sinuses, larynx, and trachea may be involved, causing obstruction, hemorrhage, or difficult intubation. Thick, immobile tongues classically develop, leading to macroGLOSSIA.\textsuperscript{1,2,5,11} MacroGLOSSIA and salivary gland involvement can produce upper airway obstruction; therefore, sedation must be titrated carefully when the airway is unprotected.\textsuperscript{1,2,5,6,9,11} Amyloid deposits can extend into the tracheobronchial tree and may result in progressive stenosis of the airways leading to difficulty with ventilation.\textsuperscript{1,2,11}

Gastrointestinal involvement is common in all forms of amyloidosis and can occur at all levels of the gastrointestinal tract.\textsuperscript{1,2,3,6,9} Malnutrition, dehydration, and gastric reflux are common; therefore, proper intravenous hydration and rapid-sequence induction are recommended.\textsuperscript{5}

Pathology related to the nervous system and tissue infiltration of amyloid fibrils presents numerous anesthetic implications. Amyloid fibrils may deposit along peripheral nerves, in autonomic ganglia, in senile plaques, or in blood vessels of the central nervous system.\textsuperscript{1,2,4,6} Peripheral neuropathy, prominent in heredofamilial amyloidosis, is a relative contraindication to regional anesthesia.\textsuperscript{5} Care with positioning is essential to prevent nerve damage and breakdown due to skin fragility and peripheral neuropathy.\textsuperscript{5} Infiltration of the autonomic nervous system may manifest as delayed gastric emptying or postural hypotension.\textsuperscript{1,2,4,5} As a result of autonomic dysfunction, the administration of anesthetic drugs to patients with familial amyloidosis increases the risk of producing significant hypotension.\textsuperscript{4,7}

Involvement of the skin is one of the most characteristic manifestations of primary amyloidosis. The face, neck, and mucosal areas may be affected, causing symptoms of hoarseness, dyspnea, and dysphagia. These symptoms may be an indicator of possible laryngeal or tracheal involvement and should be investigated further. Infiltrates of the cornea or vitreous body may be present in hereditary amyloidosis, causing visual changes.\textsuperscript{1,2}

Although liver involvement is common, liver function abnormalities are minimal and occur late in the disease. Hematologic changes may include increased fibrinolysis and selective deficiency of clotting factors,
leading to an increased risk of bleeding.\textsuperscript{1,2,5,6} Bleeding disorders are common in patients with amyloidosis, most commonly due to infiltration of blood vessels by amyloid fibrils. Acquired factor X deficiency is uncommon but is a well-documented complication of AL amyloidosis.\textsuperscript{6} Coagulopathy may contraindicate regional anesthesia.\textsuperscript{5}

Anesthetic and surgical stress cause tremendous implications for patients with amyloidosis, even during minor surgical procedures. Viana et al\textsuperscript{6} compared hemodynamics during liver transplantation in patients with familial amyloidosis with the hemodynamics in a control group. Comparison of the 2 groups revealed that standardized identical anesthetics produce significant hypotension in patients with familial amyloidosis. These patients are very sensitive to decreases in preload and require vigilant monitoring with rapid intervention. Hypotension also occurred despite adequate preload, which was treated most effectively by a vasoconstrictor infusion. Despite the decreased use of inhalation agents and opioids and increased use of vasoconstrictors, the patients with familial amyloidosis had more significant hypotensive episodes.\textsuperscript{4,7}

Amyloid fibrils are identified by biopsy of the suspected organ, abdominal fat, and renal or rectal tissue specimens, and patients often require anesthetic care. All tissues obtained must be stained with Congo red and examined under a polarizing microscope. The Congo red stain develops into a unique green when amyloid fibrils are present.\textsuperscript{1,2,5,6,9} See Figure 1B.

**Conclusion**

Amyloidosis is a complex, progressive disease, and treatment options vary depending on the type of amyloidosis present and extent of organ involvement. Liver transplantation has been available since 1990 for the treatment of familial amyloidosis. In successful transplants, normal transthyretin gradually replaces the circulating abnormal protein, followed by a gradual reduction of the existing amyloid fibrils.\textsuperscript{1,2,4,6} The most effective form of treatment for patients with AL amyloidosis is chemotherapy with stem cell transplantation. Destruction of plasma cells, with concurrent decreases in light chain production, may further prevent deposition of amyloid or even reverse the process.\textsuperscript{1,2,6} Studies have shown that outcome is related to the extent of cardiac involvement and the number of organs involved at the time of transplantation.\textsuperscript{8,9} Cardiac transplantation for severe cardiac involvement in AL and AF amyloidosis has also been successful.\textsuperscript{1,2,6,7} Subsequent stem cell transplantation is indicated after cardiac transplantation in an effort to prevent recurrent amyloid.\textsuperscript{7}

Amyloidosis has multiple implications for anesthesia providers due to the possibility of multiorgan involvement. Patients with amyloidosis are seen in the operating rooms for diagnostic, interventional, and curative purposes. Anesthesia providers must be aware of the multisystem involvement of amyloidosis and the related anesthetic implications. Each amyloidosis case is unique, and the anesthetic must be determined on a case-by-case basis and tailored to the individual signs and symptoms the patient is experiencing.

**REFERENCES**


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